

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^+).

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.

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.

- **Contingency Matrix:**

Contingency Dimension	Stimulus Event	Effect on Target Behavior	Concrete Experimental Example
Positive Reinforcement	<i>Add pleasant stimulus</i>	Increases / Maintains	Depressing a lever dispenses a sucrose pellet.
Negative Reinforcement	<i>Remove aversive stimulus</i>	Increases / Maintains	Depressing a lever terminates a continuous foot shock.
Positive Punishment	<i>Add aversive stimulus</i>	Decreases / Suppresses	Depressing a lever delivers an unexpected foot shock.
Negative Punishment	<i>Remove pleasant stimulus</i>	Decreases / Suppresses	Depressing a lever shuts off access to food pellets.

- **Neurobiological Substrates of Instrumental Action:**

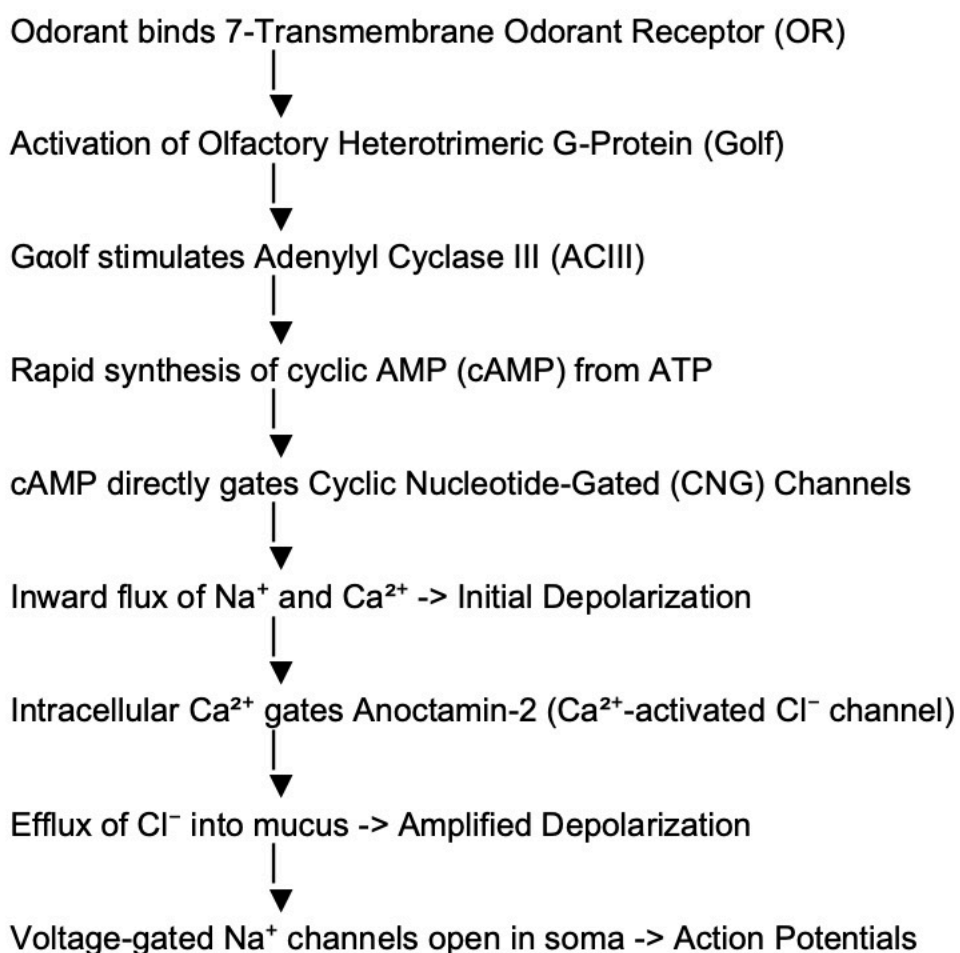
- **Prefrontal Cortex (PFC):** Mediates cognitive flexibility, goal evaluation, executive decision-making, and anticipation of behavioral consequences.
- **Dorsal Striatum (Caudate / Putamen):** Directs action selection during early acquisition and automates repetitive, over-trained actions into inflexible habits.
- **Nucleus Accumbens (Ventral Striatum):** Encodes reward magnitude, incentive salience, anticipation, and motivational drive.
- **Ventral Tegmental Area (VTA):** Sends dense dopaminergic projections into the nucleus accumbens, encoding reward prediction error signals that drive reinforcement.
- **Amygdala:** Assigns affective value, emotional salience, and positive or negative valence to environmental cues and behavioral outcomes.
- **Hippocampus:** Encodes environmental context, spatial configurations, and explicit contingency relationships between actions and outcomes.

B. The Sensory Cilia and Receptors

- Each bipolar ORN projects a single dendritic process apically to the epithelial surface, ending in an expanded knob from which 10 to 30 non-motile **cilia** project into the aqueous mucus layer.
- *Localization Proof:* Focal puff application of volatile odorants demonstrated that electrical responses are generated when stimulants contact the apical cilia, while direct application to the cell body or axonal processes elicits negligible responses.
- **The Odorant Receptor Gene Superfamily:**
 - Identified by Linda Buck and Richard Axel (1991), odorant receptors are seven-transmembrane-spanning G-protein coupled receptors.
 - Humans possess approximately 350 to 400 functional odorant receptor genes (and hundreds of pseudogenes), whereas mice maintain over 1,000 functional genes.
 - The amino acid sequences forming the transmembrane alpha-helices exhibit high sequence variability, creating variable ligand-binding pockets tailored to diverse molecular shapes, charges, and functional groups.
- **The "One Neuron – One Receptor" Rule:** Each mature olfactory receptor neuron transcribes and expresses **only a single functional odorant receptor gene** from its genomic repertoire.

6. Olfactory Transduction Cascade

The biochemical signaling cascade within olfactory cilia transforms chemical binding into electrical depolarization:



B. Early-LTP (E-LTP): Post-Translational Modifications and AMPA Trafficking

- **Enzyme Activation:** Elevated spine calcium activates **CaMKII** and **Protein Kinase C (PKC)**.
- **CaMKII Autophosphorylation:** Activated CaMKII undergoes autonomous autophosphorylation at Threonine-286, sustaining its enzymatic activity after free calcium drops.
- **Target Actions:**
 - Phosphorylates existing synaptic AMPA receptor subunits (GluA1), increasing their single-channel conductance.
 - Promotes the exocytosis and lateral membrane diffusion of intracellular AMPA receptor pools into the postsynaptic density.
- **Recruitment to "Silent Synapses":** Immature or resting synapses that express surface NMDA receptors but lack functional AMPA receptors generate no baseline EPSP at resting potentials ("silent"). LTP induction mobilizes AMPA receptors into these postsynaptic densities, rendering them functionally responsive to baseline glutamate release.

C. Late-LTP (L-LTP): Protein Synthesis and Structural Remodeling

- **Requirement for Translation and Transcription:** While E-LTP (lasting 1–3 hours) relies on pre-existing proteins and post-translational phosphorylation, L-LTP (persisting for days, weeks, or months) requires de novo gene transcription and mRNA translation.
- **Pharmacological Inhibition:** Administering protein synthesis inhibitors (e.g., anisomycin, cycloheximide) does not block initial LTP induction, but causes potentiated responses to decay back to baseline within 2 to 4 hours.
- **Structural Plasticity:** Sustained signaling activates **CREB-mediated gene expression**, generating structural remodeling proteins that enlarge existing dendritic spine heads and induce new dendritic spines along the dendritic shaft.

6. Long-Term Depression (LTD) and Spike-Timing-Dependent Plasticity (STDP)

