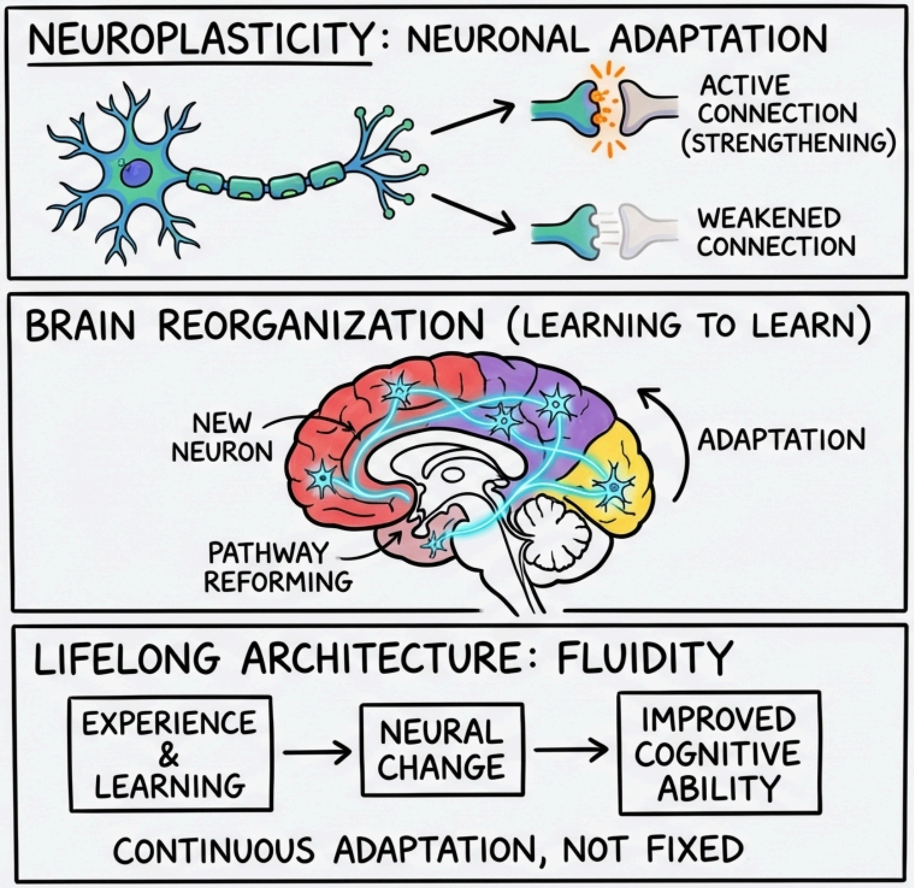
Neural Plasticity

Neural Plasticity: How Brains Learn to Learn Neural Plasticity Visual Summary LECTURE OUTLINE (80 minutes) I. Cajal's Paradox & Foundation Review (20 min) • Fixed architecture vs. dynamic function • Neural architecture, electrical & chemical signaling recap • Homosynaptic vs heterosynaptic plasticity II. Long-Term Potentiation & Depression (15 min) • Bliss & Lømo's 1973 discovery • NMDA receptors as coincidence detectors • LTD and the pianist who couldn't forget III. Molecular Machinery of Memory (20 min) • Spike-timing dependent plasticity (STDP) • Structural plasticity: dendritic spines • Metaplasticity: learning how to learn IV. Critical Periods & Development (10 min) • Hubel & Wiesel's kittens • Genie's tragedy and language acquisition • Indigenous songlines and perfect pitch V. Adult Neurogenesis & Repair (8 min) • 2000 new neurons daily • London taxi drivers and cortical remapping

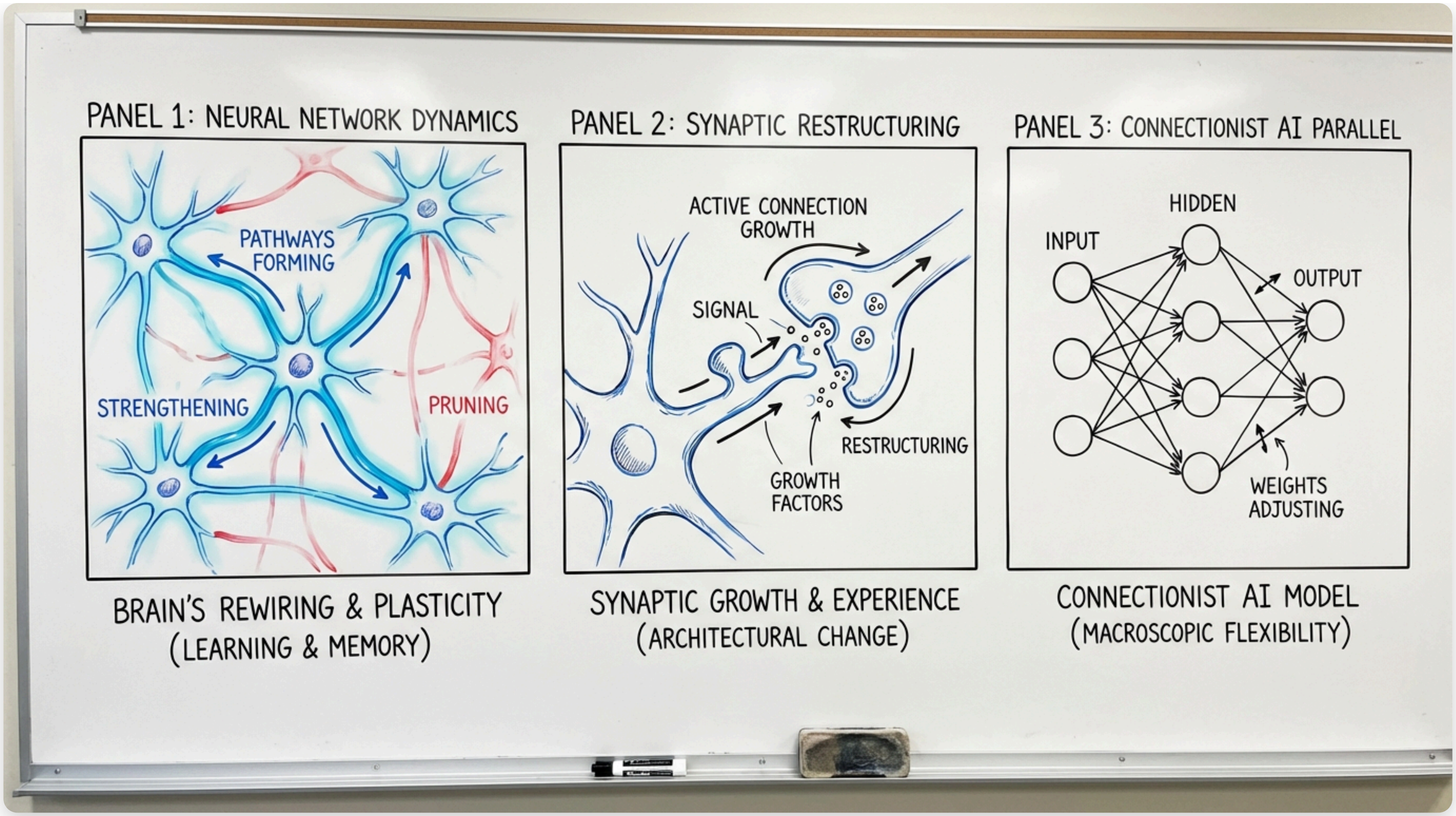
- Here are 5 main points from the text:
- The brain's structure is dynamic and continuously changes throughout life.
- Learning and memory involve processes that strengthen or weaken connections between brain cells.
- Learning also involves precise molecular and structural changes within brain cells, such as altered connections.
- The brain has specific "critical periods" during development when it is highly ready to learn certain skills.
- Even adult brains can generate new cells and reorganize existing parts based on new experiences.


NEUROPLASTICITY: NEURONAL ADAPTATION
ACTIVE CONNECTION (STRENGTHENING)
WEAKENED CONNECTION
BRAIN REORGANIZATION (LEARNING TO LEARN)
NEW NEURON
ADAPTATION
PATHWAY REFORMING
LIFELONG ARCHITECTURE: FLUIDITY
EXPERIENCE & LEARNING
NEURAL CHANGE
IMPROVED COGNITIVE ABILITY
CONTINUOUS ADAPTATION, NOT FIXED

Brain Plasticity

VI. Learning in Real Networks (7 min) • Memory consolidation and reconsolidation • AI/connectionism parallels and differences Your thoughts move at 120 meters per second, but your brain rewrites itself at the speed of experience. Today we resolve Santiago Ramón y Cajal's paradox: how apparently fixed neural structures create infinite flexibility. You'll discover that every word you hear is literally changing the physical structure of your synapses, that learning a new skill grows new brain tissue, and that forgetting is as precisely controlled as remembering. Through the molecular choreography of long-term potentiation, we'll see how calcium influx triggers protein synthesis that locks memories into synaptic architecture. We'll explore why critical periods exist—and how to reopen them—why sleep is essential for spine pruning, and how your morning coffee affects the plasticity rules governing this very moment. From bacterial action potentials to human consciousness, from Hebbian learning to artificial intelligence, we'll trace the 3.8-billion-year evolution of learning itself. Prepare to understand why you can't tickle yourself, how meditation physically changes brain structure, and why every experience leaves its mark—but not equally.

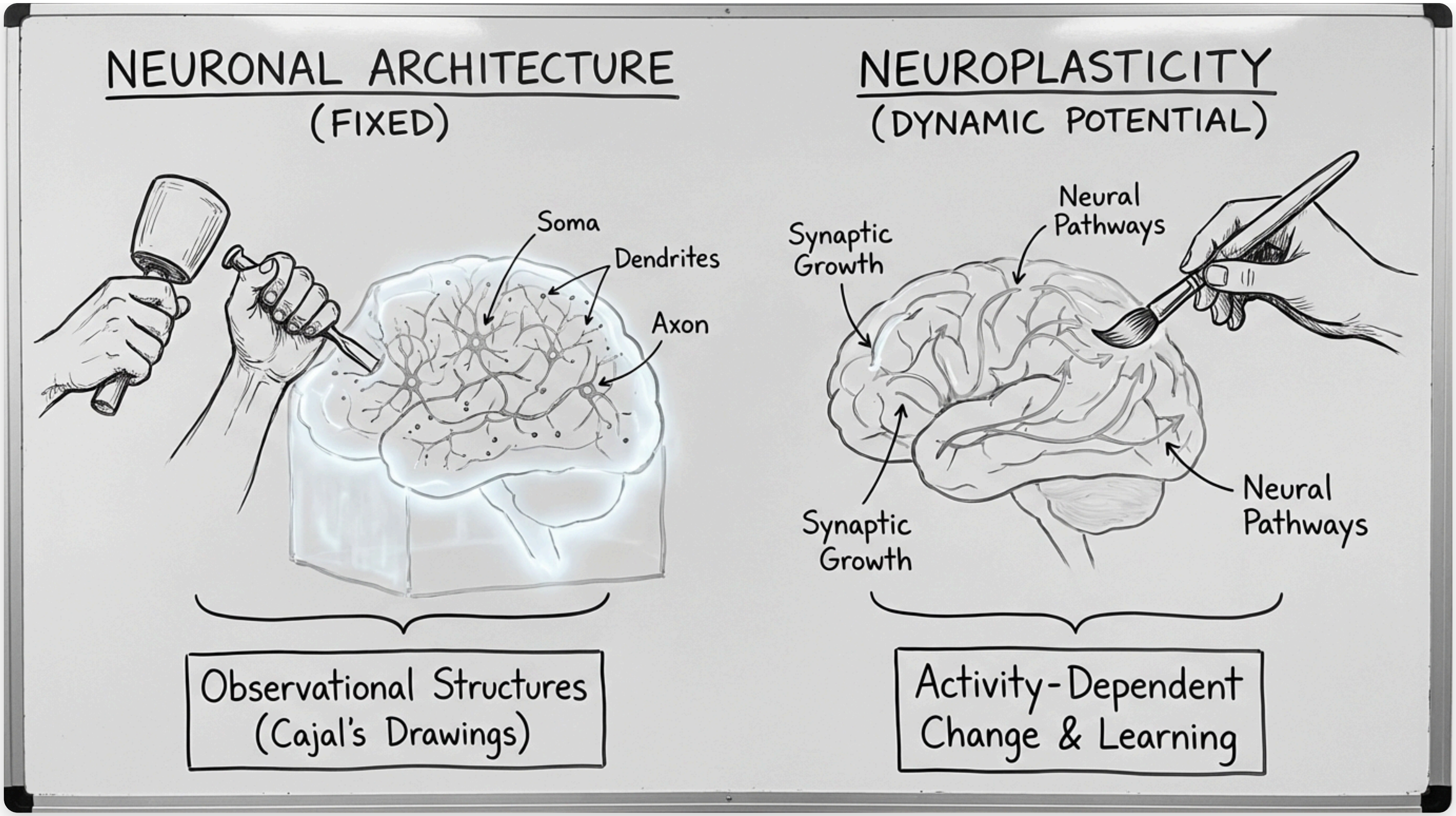
> → Here are 3-5 main points from the text:
> → Your brain constantly changes its physical structure based on your experiences.
> → Learning and memory involve specific molecular processes that strengthen synaptic connections.
> → Forgetting memories is an active and controlled process, just like remembering.
> → Daily habits, such as sleep and drinking coffee, affect how your brain changes and learns.


PANEL 1: NEURAL NETWORK DYNAMICS
PATHWAYS FORMING
STRENGTHENING
PRUNING
BRAIN'S REWIRING & PLASTICITY
(LEARNING & MEMORY)
PANEL 2: SYNAPTIC RESTRUCTURING
ACTIVE CONNECTION GROWTH
SIGNAL
RESTRUCTURING
GROWTH FACTORS
SYNAPTIC GROWTH & EXPERIENCE
(ARCHITECTURAL CHANGE)
PANEL 3: CONNECTIONIST AI PARALLEL
HIDDEN
INPUT
OUTPUT
WEIGHTS ADJUSTING
CONNECTIONIST AI MODEL
(MACROSCOPIC FLEXIBILITY)

Sculpting The Brain

Today's journey: From Cajal's 1894 drawings to 2024's real-time spine imaging. We'll discover how your brain sculpts itself using experience as both chisel and blueprint. Opening: Cajal's Paradox Look at this drawing. Santiago Ramón y Cajal spent thousands of hours at his microscope, using a technique he'd modified from Camillo Golgi, staining neurons with silver nitrate to reveal their architecture. Cajal saw what looked like fixed sculptures—beautiful, permanent, unchangeable structures frozen in biological glass. The neurons he drew in 1894 looked exactly like the neurons he drew in 1904. Yet this same man wrote something that should have been impossible given what he was seeing: "Every man can, if he so desires, become the sculptor of his own brain."

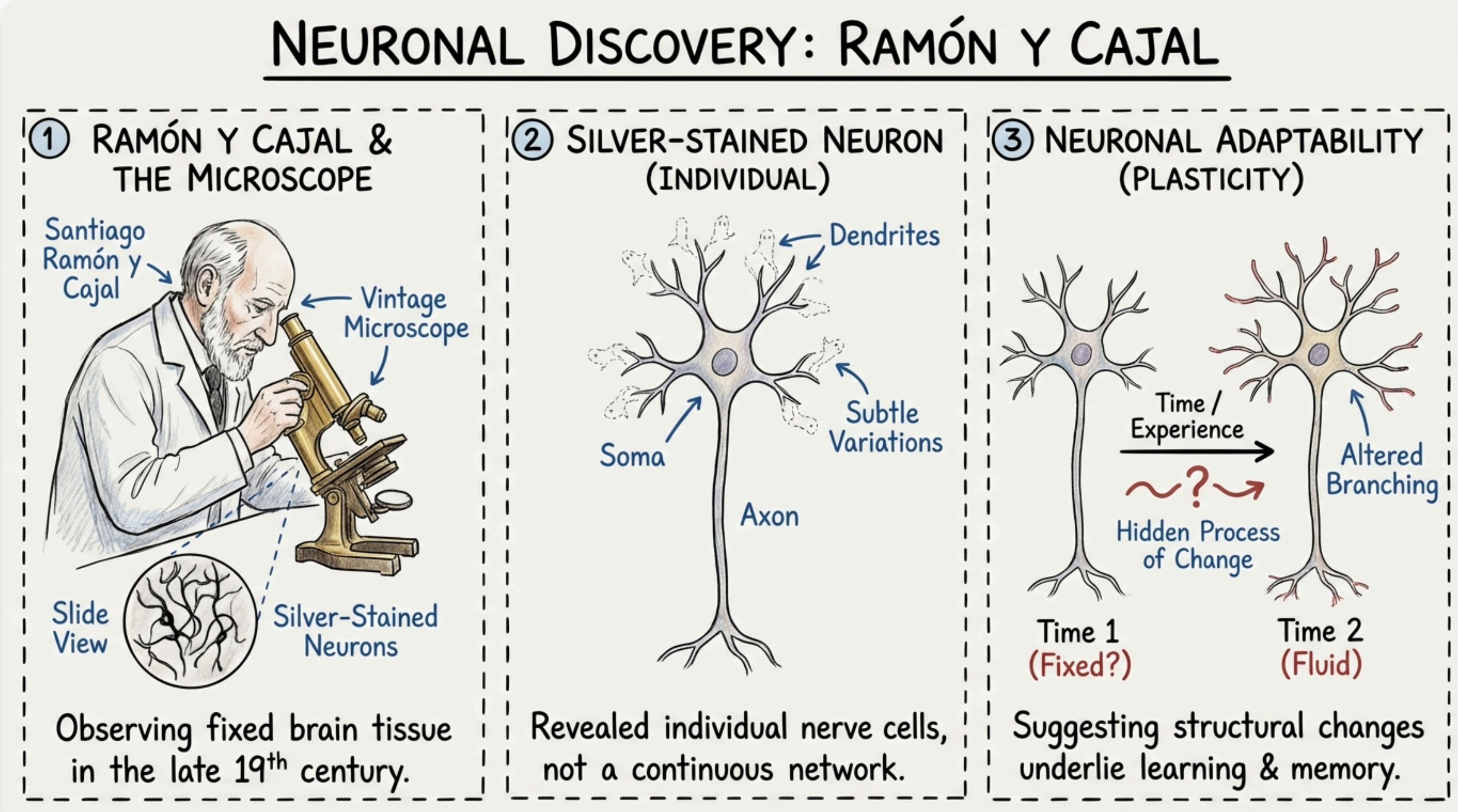
> → Here are 3 main points from the text:
>
> → The brain continuously shapes itself based on an individual's experiences.
>
> → Early scientist Santiago Ramón y Cajal observed that brain cells appeared fixed and unchangeable under his microscope.
>
> → Despite his observations, Cajal believed individuals could actively change and improve their own brains.


NEURONAL ARCHITECTURE
(FIXED)
NEUROPLASTICITY
(DYNAMIC POTENTIAL)
Soma
Dendrites
Axon
Synaptic Growth
Neural Pathways
Synaptic Growth
Neural Pathways
Observational Structures (Cajal's Drawings)
Activity-Dependent Change & Learning

Brain Plasticity

How could Cajal believe in brain sculpting when he was staring at apparently fixed architecture? He had noticed something peculiar in his preparations—neurons from musicians had denser dendritic trees in motor areas, neurons from scholars showed elaborations in association cortices, and most mysteriously, neurons from young animals looked different from old ones even when stained identically. The structure was stable, yes, but something about the connections, their strength, their efficacy, was fluid. Cajal was seeing the shadows of plasticity without having the tools to measure it directly.

- → Cajal noticed that the brains of musicians and scholars showed structural differences based on their activities.
- → He also observed that neurons from young animals looked different from those in older animals.
- → Cajal realized that while brain structure seemed stable, the connections between neurons were fluid and changeable.
- → He was observing early signs of brain plasticity, even though he lacked the tools to measure it directly.

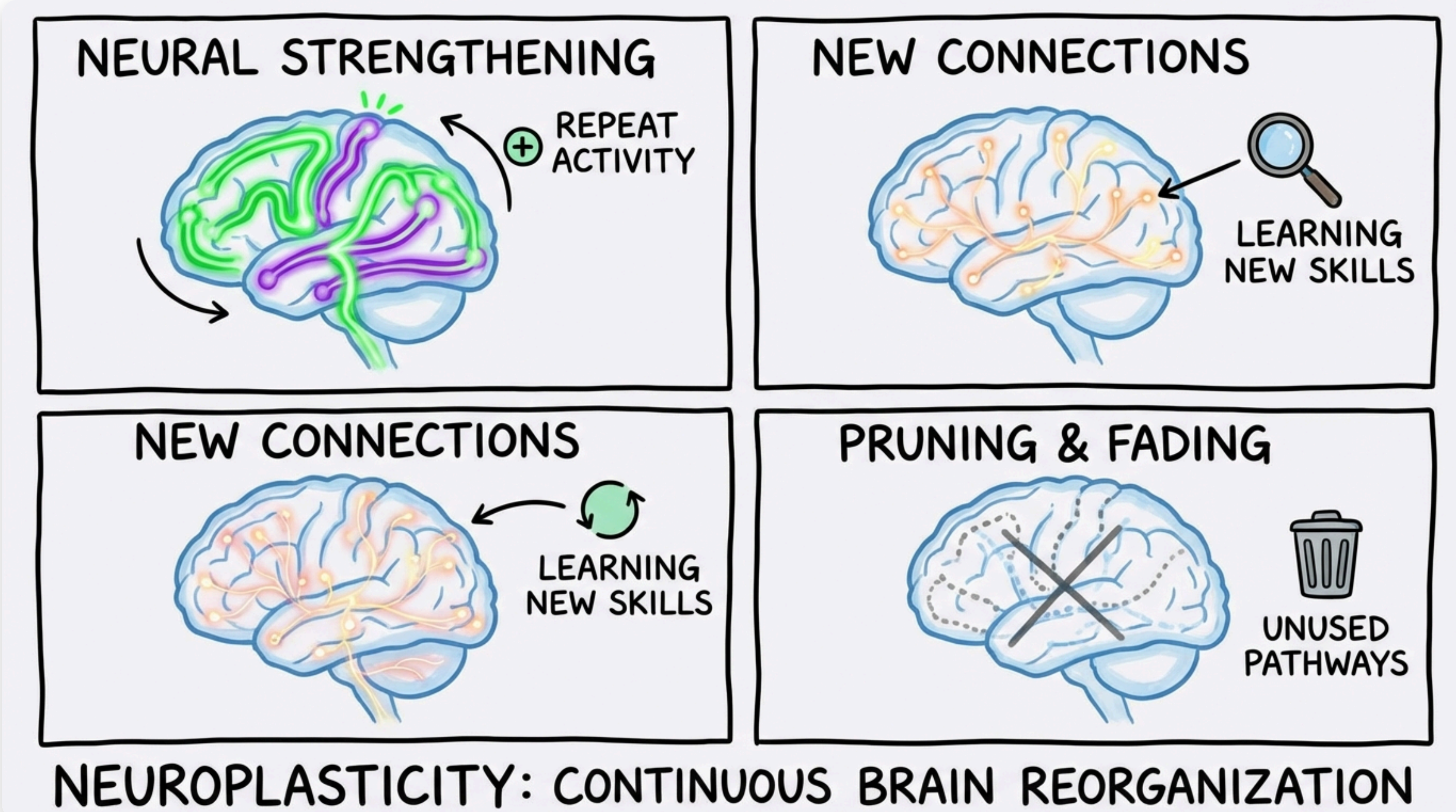


NEURONAL DISCOVERY: RAMÓN Y CAJAL
1 RAMÓN Y CAJAL & THE MICROSCOPE
Santiago Ramón y Cajal
Vintage Microscope
Slide View
Silver-Stained Neurons
Observing fixed brain tissue in the late 19th century.
2 SILVER-STAINED NEURON (INDIVIDUAL)
Dendrites
Soma
Subtle Variations
Axon
Revealed individual nerve cells, not a continuous network.
3 NEURONAL ADAPTABILITY (PLASTICITY)
Time / Experience
?
Hidden Process of Change
Altered Branching
Time 1 (Fixed?)
Time 2 (Fluid)
Suggesting structural changes underlie learning & memory.

Brain Plasticity

Today, we're going to discover how your brain is rewriting itself at this very moment. Every word I speak, every concept you grasp, every moment of confusion followed by clarity—all of these are literally changing the physical structure of your neural connections. Neural plasticity, or neuroplasticity, refers to the brain's ability to reorganize itself by forming new neural connections throughout life. You walked into this room with one brain, and you'll leave with another. The question isn't whether your brain will change during this lecture—it's how much, where, and whether those changes will last until tomorrow. The paradox that tortured Cajal has been resolved, but the answer is more extraordinary than he imagined. Your neurons mostly stay where they are—he was right about that—but their connections dance, strengthen, weaken, appear, and disappear in a choreography that makes you who you are. The Symphony We've Built So Far Neural Architecture Review

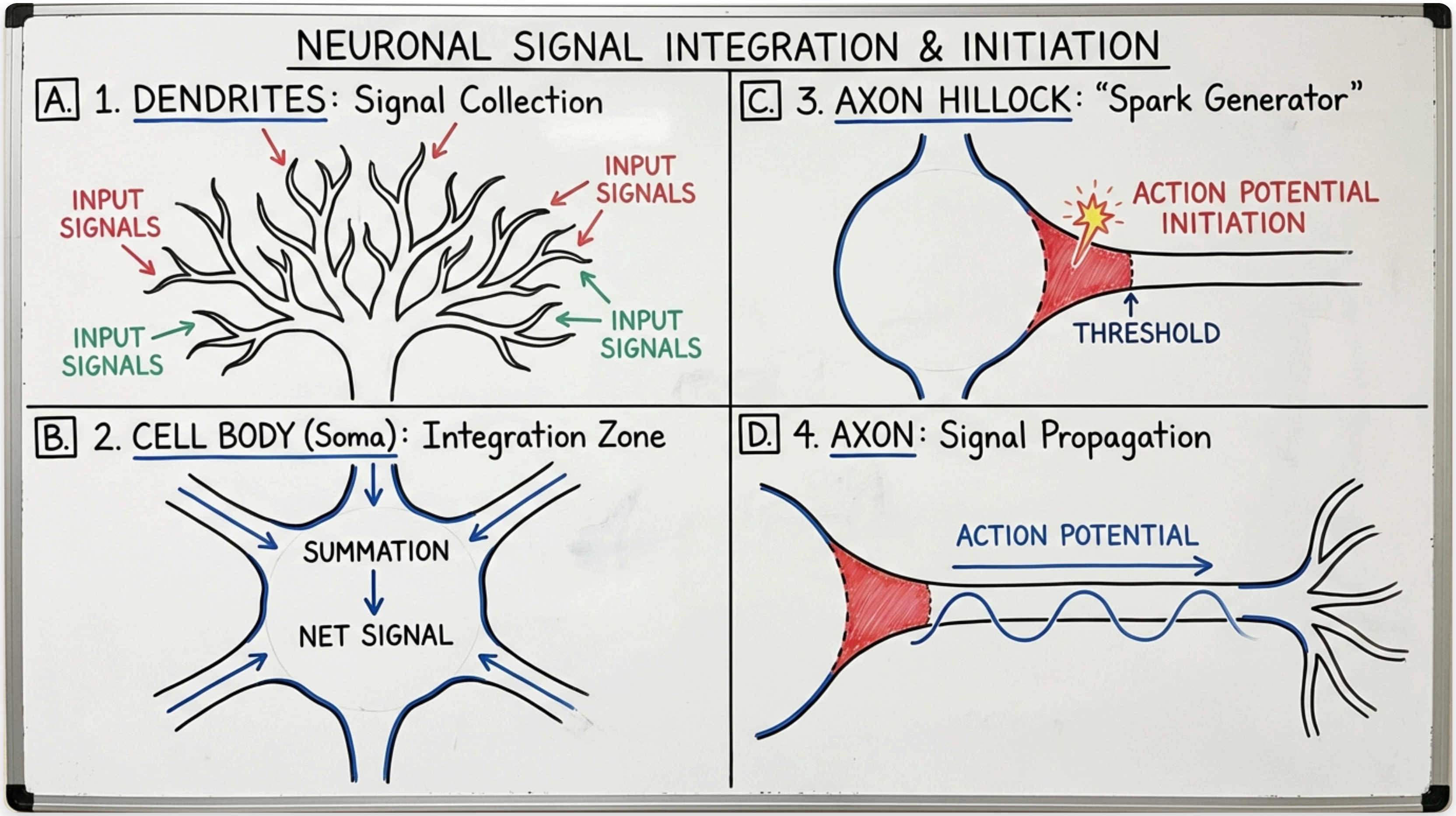
- Here are 4 main points from the text:
- Your brain constantly changes its physical structure.
- Neuroplasticity is the brain's ability to reorganize itself by forming new connections throughout life.
- Every experience and new concept you learn literally changes your neural connections.
- Individual neurons generally stay in place, but their connections constantly strengthen, weaken, or disappear.


NEURAL STRENGTHENING
REPEAT ACTIVITY
NEW CONNECTIONS
LEARNING NEW SKILLS
NEW CONNECTIONS
LEARNING NEW SKILLS
PRUNING & FADING
UNUSED PATHWAYS
NEUROPLASTICITY: CONTINUOUS BRAIN REORGANIZATION

Neural Signal Integration

Let's reconstruct what we know about the hardware that makes plasticity possible. The dendrites are the listeners of the neural world, spreading like roots to collect whispers from thousands of other neurons. Each dendritic branch acts as an antenna, but not a passive one—these structures perform spatial and temporal summation, adding signals that arrive at nearby locations or in quick succession. The cell body, or soma, serves as the integration zone where all these whispers get tallied into a single decision: fire or don't fire. The axon hillock, that specialized region where the axon emerges, has the lowest threshold for action potential generation—it's the spark generator, the point of no return.

> → Here are 4 main points from the text:
>
> → Dendrites act as antennas, collecting signals from many other neurons.
>
> → These dendritic branches add up signals that arrive at nearby locations or in quick succession.
>
> → The cell body integrates all these signals to decide whether the neuron fires.
>
> → The axon hillock then generates the electrical impulse, or action potential, for the neuron.


NEURONAL SIGNAL INTEGRATION & INITIATION
A. 1. DENDRITES: Signal Collection
INPUT SIGNALS
INPUT SIGNALS
INPUT SIGNALS
INPUT SIGNALS
C. 3. AXON HILLOCK: "Spark Generator"
ACTION POTENTIAL INITIATION
THRESHOLD
B. 2. CELL BODY (Soma): Integration Zone
SUMMATION
NET SIGNAL
D. 4. AXON: Signal Propagation
ACTION POTENTIAL

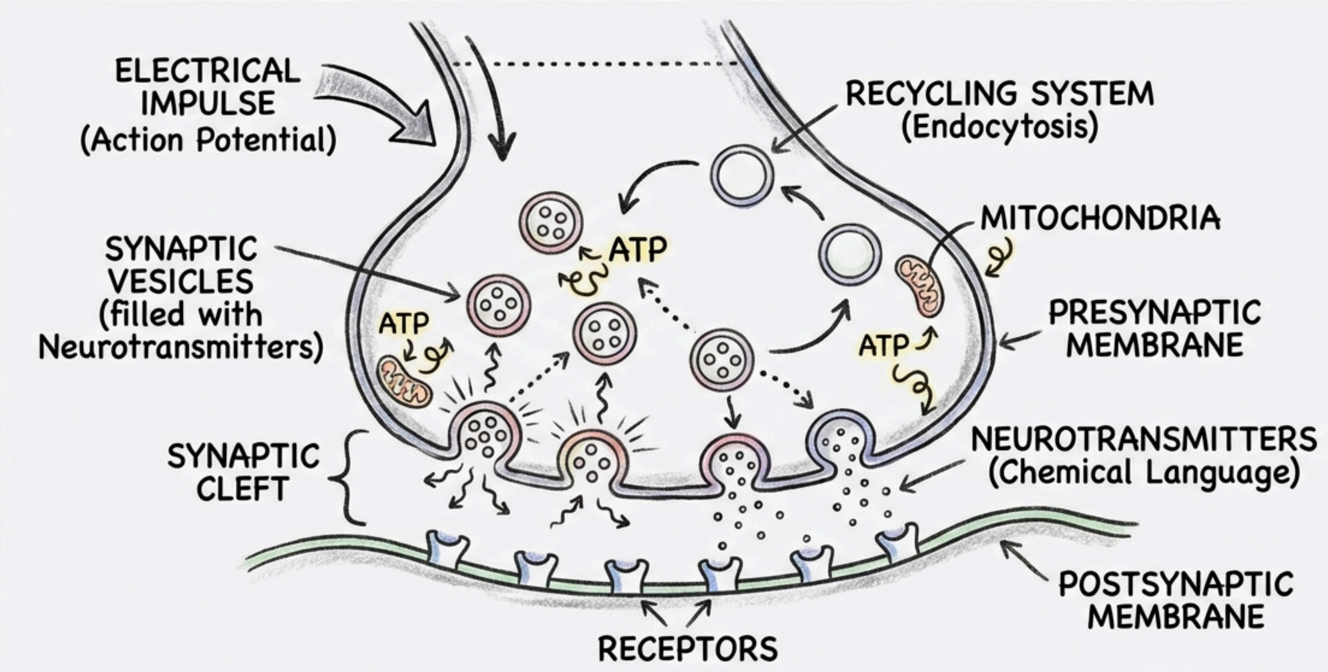
Axon Terminal Function

The axon terminal is where the electrical signal gets translated into chemical language. This isn't just a wire touching another wire—it's a sophisticated broadcasting station with pools of vesicles ready to release, specialized machinery for fusion, and recycling systems to sustain transmission. Each component is optimized for the fundamental trade-off of the nervous system: information processing versus energy consumption. Your brain uses 20% of your body's energy budget to maintain these structures and their activity.

- Here are 4 main points from the text:
- The axon terminal converts electrical signals into chemical signals.
- It is a complex system with vesicles, specialized machinery, and recycling systems.
- Each part of the axon terminal is optimized for processing information and using energy efficiently.
- The brain uses 20% of the body's energy to maintain these structures and their activity.

NEURON AXON TERMINAL: ORGANIC BROADCASTING STATION

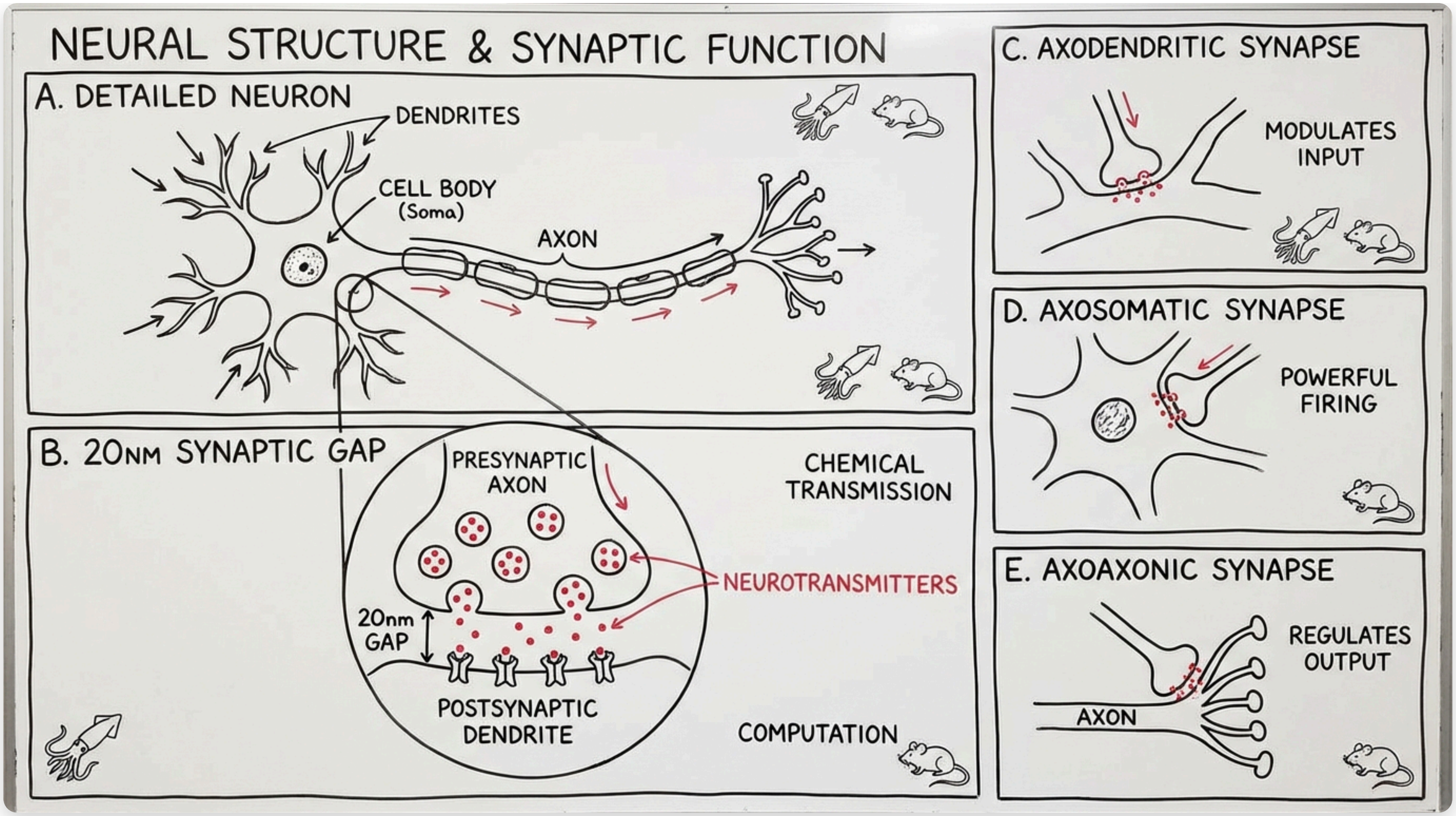
PANEL 1: SYNAPTIC TRANSMISSION (HIGH-ENERGY)



Synapse Types

Chemical Transmission Mastery The synaptic gap is only 20 nanometers wide—that's 5,000 times thinner than a human hair—but it's where the real computation happens. The nervous system has three types of synapses, each with different computational roles. Axodendritic synapses, the most common, allow modulation of input signals before they reach the cell body. Axosomatic synapses, landing directly on the cell body, have powerful, immediate effects on whether a neuron fires. Axoaxonic synapses are the modulators, sitting on other synapses to regulate their function—these mediate the heterosynaptic plasticity we'll explore today.

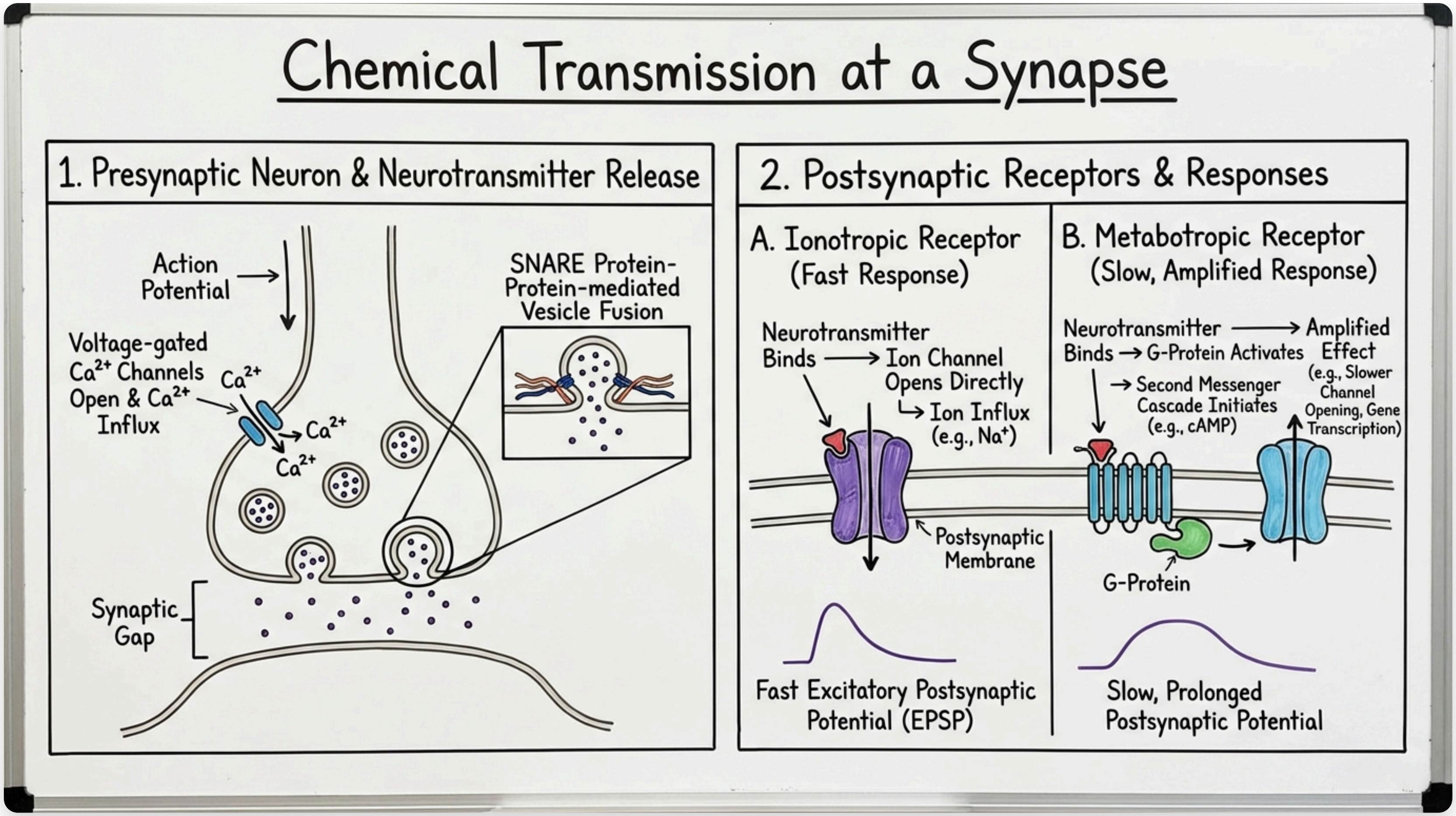
- Main Points:
- The synaptic gap performs the brain's main computations.
- The nervous system contains three different types of synapses.
- Axodendritic synapses adjust input signals before they reach a neuron's body.
- Axosomatic synapses directly determine if a neuron fires.
- Axoaxonic synapses regulate the function of other synapses.


NEURAL STRUCTURE & SYNAPTIC FUNCTION
A. DETAILED NEURON
DENDRITES
CELL BODY (Soma)
AXON
B. 20NM SYNAPTIC GAP
PRESYNAPTIC AXON
CHEMICAL TRANSMISSION
NEUROTRANSMITTERS
20nm GAP
POSTSYNAPTIC DENDRITE
COMPUTATION
C. AXODENDRITIC SYNAPSE
MODULATES INPUT
D. AXOSOMATIC SYNAPSE
POWERFUL FIRING
E. AXOAXONIC SYNAPSE
REGULATES OUTPUT
AXON

Chemical Transmission

Chemical Transmission Mastery When an action potential reaches the terminal, voltage-gated calcium channels open, and calcium rushes in. This calcium binds to sensor proteins that trigger SNARE proteins to zip together, pulling vesicle membranes into the presynaptic membrane and dumping neurotransmitter into the gap. The elegance is in the receptor types on the other side: ionotropic receptors like AMPA and NMDA for glutamate, or GABA-A for inhibition, directly open ion channels for fast responses. Metabotropic receptors like mGluR or GABA-B trigger second messenger cascades, trading speed for amplification and duration. The Plasticity Revolution: How Experience Becomes Structure Two Forms of Synaptic Plasticity

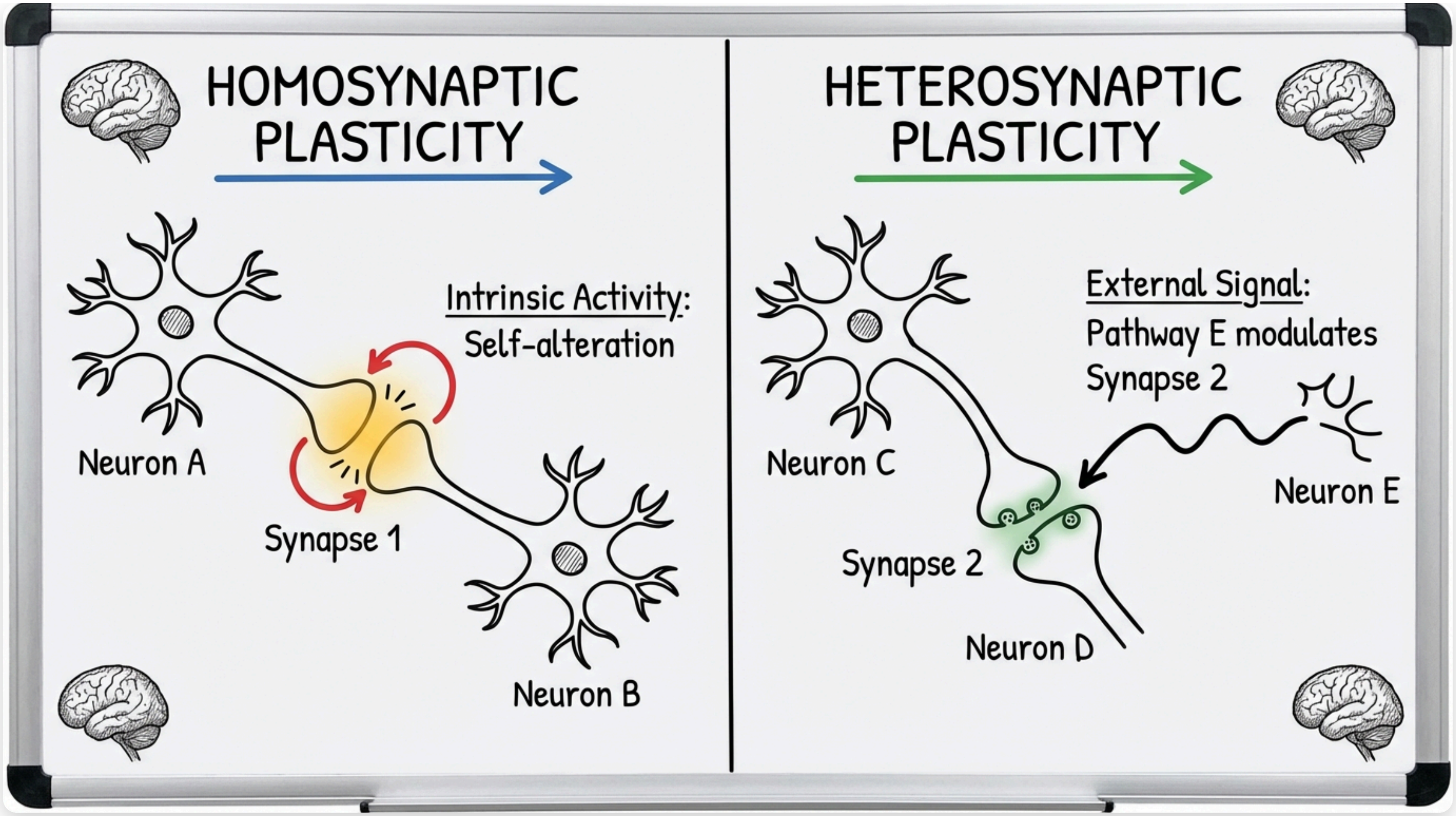
> → Here are 3 main points from the text:
>
> → When an action potential reaches the nerve terminal, calcium enters and triggers the release of neurotransmitters.
>
> → Ionotropic receptors directly open ion channels, creating fast responses in the cell.
>
> → Metabotropic receptors trigger second messenger cascades, producing effects that are slower but last longer and are amplified.


Chemical Transmission at a Synapse
1. Presynaptic Neuron & Neurotransmitter Release
Action Potential
Voltage-gated Ca^{2+} Channels Open & Ca^{2+} Influx
Ca^{2+}
Ca^{2+}
Ca^{2+}
SNARE Protein-Protein-mediated Vesicle Fusion
Synaptic Gap
2. Postsynaptic Receptors & Responses
A. Ionotropic Receptor (Fast Response)
Neurotransmitter Binds → Ion Channel Opens Directly
↳ Ion Influx (e.g., Na^{+})
Postsynaptic Membrane
Fast Excitatory Postsynaptic Potential (EPSP)
B. Metabotropic Receptor (Slow, Amplified Response)
Neurotransmitter Binds → G-Protein Activates → Amplified Effect
(e.g., Slower Channel Opening, Gene Transcription)
→ Second Messenger Cascade Initiates (e.g., cAMP)
G-Protein
Slow, Prolonged Postsynaptic Potential

Synaptic Plasticity Forms

Chemical Transmission Mastery The word "plasticity" comes from the Greek "plastikos," meaning "capable of being shaped or molded." In the nervous system, we see two fundamental forms of this moldability. Homosynaptic or intrinsic plasticity refers to changes in synaptic strength brought about by the synapse's own activity—the synapse modifies itself based on its own history. Heterosynaptic or extrinsic plasticity involves changes triggered by activity in other pathways—the synapse is modified by external influences. These mechanisms of synaptic plasticity include changes in the strength of connections between neurons through processes like long-term potentiation (LTP) and long-term depression (LTD).

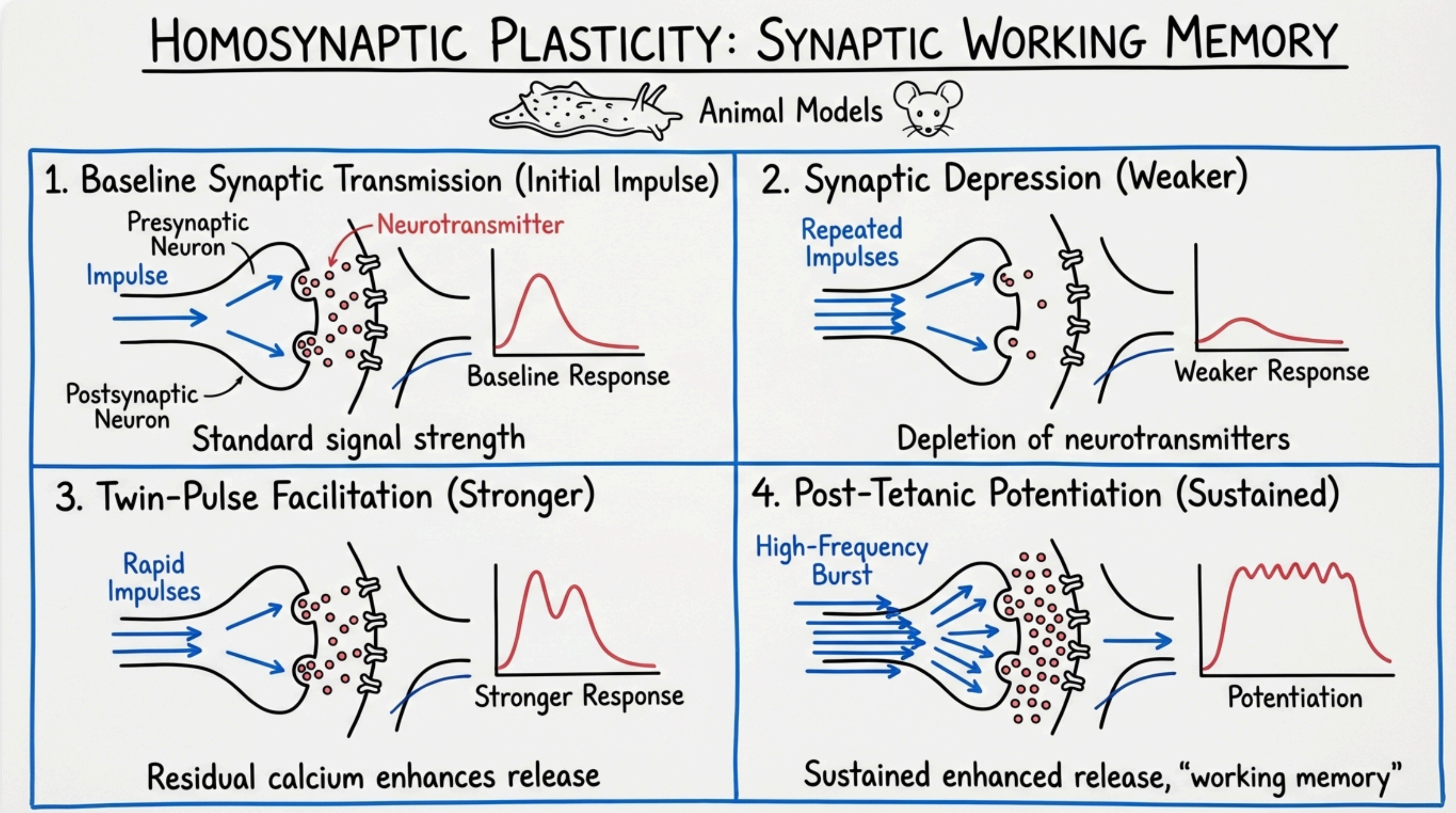
- Plasticity means something can be shaped or molded.
- The nervous system shows two main types of plasticity.
- Homosynaptic plasticity occurs when a synapse changes based on its own activity.
- Heterosynaptic plasticity happens when other pathways' activity changes a synapse.
- Synaptic plasticity changes the strength of connections between neurons, for example through long-term potentiation (LTP) and long-term depression (LTD).


HOMOSYNAPTIC PLASTICITY
Intrinsic Activity:
Self-alteration
Neuron A
Synapse 1
Neuron B
HETEROSYNAPTIC PLASTICITY
External Signal:
Pathway E modulates Synapse 2
Neuron C
Neuron E
Synapse 2
Neuron D

Homosynaptic Plasticity

Chemical Transmission Mastery Let me demonstrate homosynaptic plasticity with a simple experiment we've replicated thousands of times. Stimulate a sensory neuron once, and it produces a 1 millivolt EPSP in its target motor neuron. Stimulate it again 200 milliseconds later, and the second EPSP is only 0.7 millivolts—this is synaptic depression, caused by depletion of readily-releasable vesicles. But if you wait just 20 milliseconds between stimuli, the second EPSP is 2 millivolts—this is twin-pulse facilitation, caused by residual calcium from the first pulse adding to calcium from the second. Post-tetanic potentiation takes this further. Deliver a rapid train of stimuli—a tetanus—and the synapse remains strengthened for minutes afterward, even after the calcium has returned to baseline. The synapse remembers its recent intensive use. These short-term changes are the working memory of synapses, holding information temporarily while longer-term mechanisms decide what's worth keeping.

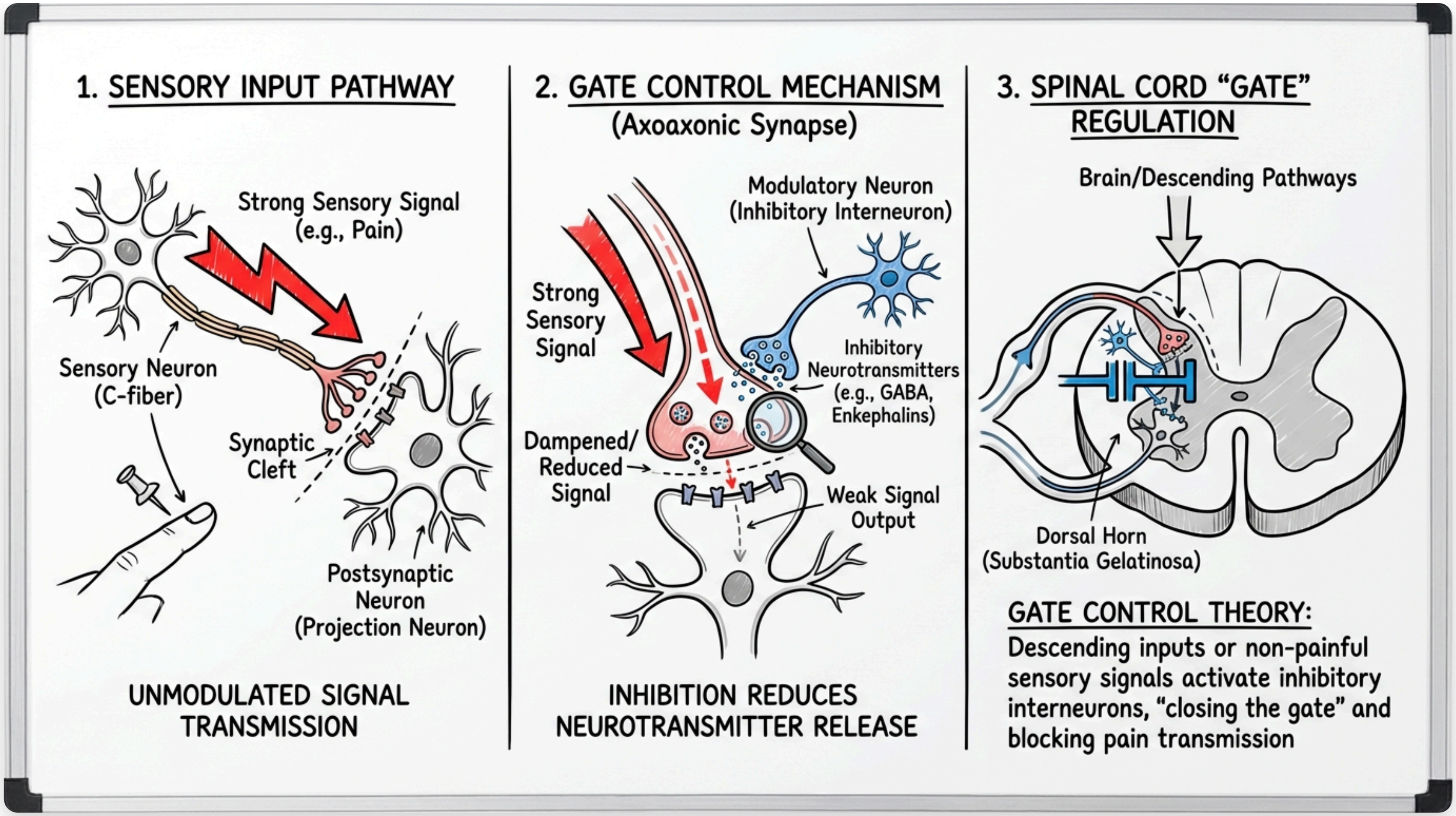
- Main Points:
- A neuron's signal weakens if it is stimulated again after a short delay. This weakening is called synaptic depression.
- Closely spaced stimulations make a neuron's signal stronger. This twin-pulse facilitation happens because calcium from the first pulse adds to the second.
- A rapid burst of stimuli can strengthen a synapse for several minutes. This effect is known as post-tetanic potentiation.
- These short-term changes in synapses act as a working memory. They temporarily hold information.


Homosynaptic Plasticity: Synaptic Working Memory
Animal Models
1. Baseline Synaptic Transmission (Initial Impulse)
Presynaptic Neuron
Neurotransmitter
Impulse
Postsynaptic Neuron
Baseline Response
Standard signal strength
2. Synaptic Depression (Weaker)
Repeated Impulses
Weaker Response
Depletion of neurotransmitters
3. Twin-Pulse Facilitation (Stronger)
Rapid Impulses
Stronger Response
Residual calcium enhances release
4. Post-Tetanic Potentiation (Sustained)
High-Frequency Burst
Potentiation
Sustained enhanced release, "working memory"

Presynaptic Control

Chemical Transmission Mastery Heterosynaptic plasticity adds another layer of control. A modulatory neuron making an axoaxonic synapse can dial transmission up or down without itself directly exciting or inhibiting the postsynaptic cell. In the spinal cord, descending signals use presynaptic inhibition to filter sensory input before it reaches the brain—this is why rubbing an injury reduces pain. The gate is controlled before the signal enters. Donald Hebb crystallized the principle in 1949: "Cells that fire together, wire together." But he couldn't have imagined the molecular machinery that would validate his prophecy. Long-Term Potentiation: The Discovery That Changed Everything

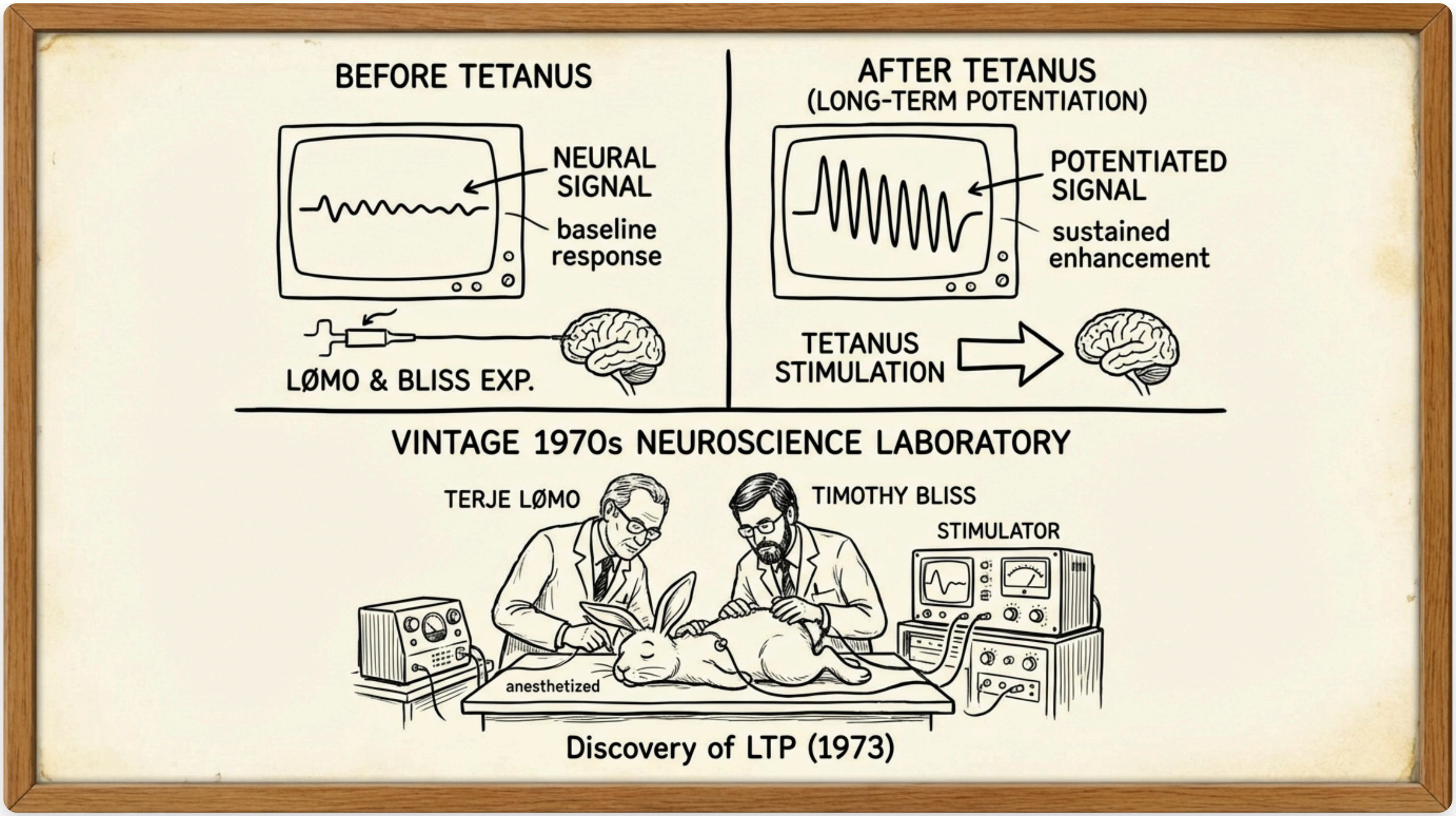
- Main Points:
- Heterosynaptic plasticity offers an additional method for controlling chemical signals between neurons.
- Modulatory neurons use axoaxonic synapses to adjust the strength of nerve signals indirectly.
- The spinal cord uses presynaptic inhibition to filter sensory input, explaining why rubbing an injury reduces pain.
- Donald Hebb introduced the principle "Cells that fire together, wire together" in 1949.


1. SENSORY INPUT PATHWAY
Strong Sensory Signal (e.g., Pain)
Sensory Neuron (C-fiber)
Synaptic Cleft
Postsynaptic Neuron (Projection Neuron)
UNMODULATED SIGNAL TRANSMISSION
2. GATE CONTROL MECHANISM (Axoaxonic Synapse)
Modulatory Neuron (Inhibitory Interneuron)
Strong Sensory Signal
Inhibitory Neurotransmitters (e.g., GABA, Enkephalins)
Dampened/ Reduced Signal
Weak Signal Output
INHIBITION REDUCES NEUROTRANSMITTER RELEASE
3. SPINAL CORD "GATE" REGULATION
Brain/Descending Pathways
Dorsal Horn (Substantia Gelatinosa)
GATE CONTROL THEORY:
Descending inputs or non-painful sensory signals activate inhibitory interneurons, "closing the gate" and blocking pain transmission

Long-Term Potentiation

Chemical Transmission Mastery In 1973, two researchers in Oslo forever changed how we think about memory. Terje Lømo and Timothy Bliss were working with anesthetized rabbits, recording from the dentate gyrus while stimulating the perforant path from the entorhinal cortex. They would deliver a test stimulus every few seconds, recording a stable EPSP of about 2 millivolts. Then they delivered their tetanus—100 pulses at 100 Hz, a mere one second of intense stimulation. What happened next seemed impossible. The same test stimulus that had produced 2 millivolt EPSPs before the tetanus now produced 5 millivolt responses. More remarkably, this enhancement lasted for hours, sometimes days. They had discovered long-term potentiation—LTP—the first physiological phenomenon with the staying power necessary to explain memory.

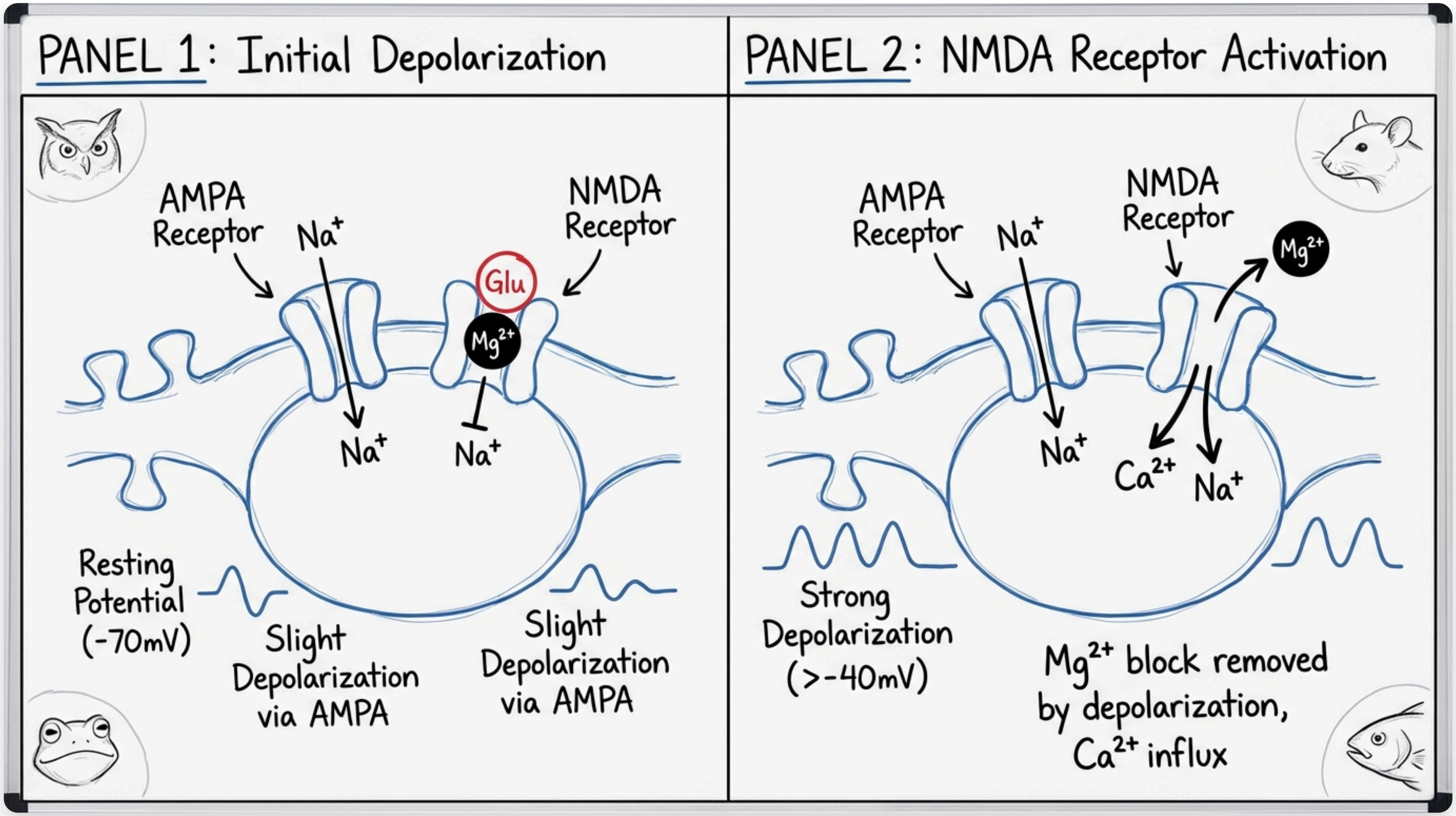
> - Here are 4 main points from the text:
> - In 1973, Lømo and Bliss discovered long-term potentiation (LTP).
> - They studied memory by stimulating brain cells in anesthetized rabbits.
> - A brief, intense stimulation made nerve cells respond much more strongly to regular signals.
> - This enhanced response lasted for a long time, helping to explain how memories are formed and stored.


BEFORE TETANUS
NEURAL SIGNAL
baseline response
LØMO & BLISS EXP.
AFTER TETANUS
(LONG-TERM POTENTIATION)
POTENTIATED SIGNAL
sustained enhancement
TETANUS STIMULATION
VINTAGE 1970s NEUROSCIENCE LABORATORY
TERJE LØMO
TIMOTHY BLISS
STIMULATOR
anesthetized
Discovery of LTP (1973)

NMDA Coincidence Detector

The NMDA Receptor: Nature's Coincidence Detector Let me show you the molecular choreography that makes LTP possible. The postsynaptic spine at a typical CA3 to CA1 synapse in the hippocampus contains two types of glutamate receptors. AMPA receptors are straightforward—glutamate binds, the channel opens, sodium enters, causing depolarization. But NMDA receptors are molecular coincidence detectors with an elegant trick. At resting potential, a magnesium ion sits in the channel pore like a cork in a bottle. Even if glutamate binds, no current flows—the magnesium blocks everything. During weak stimulation, only AMPA receptors contribute to the response. But during a tetanus, something beautiful happens. The temporal and spatial summation of many inputs depolarizes the postsynaptic membrane significantly. As the inside of the cell becomes less negative, reaching about -35 millivolts, the magnesium ion is electrically repelled from its binding site. The NMDA channel opens, and calcium floods in.

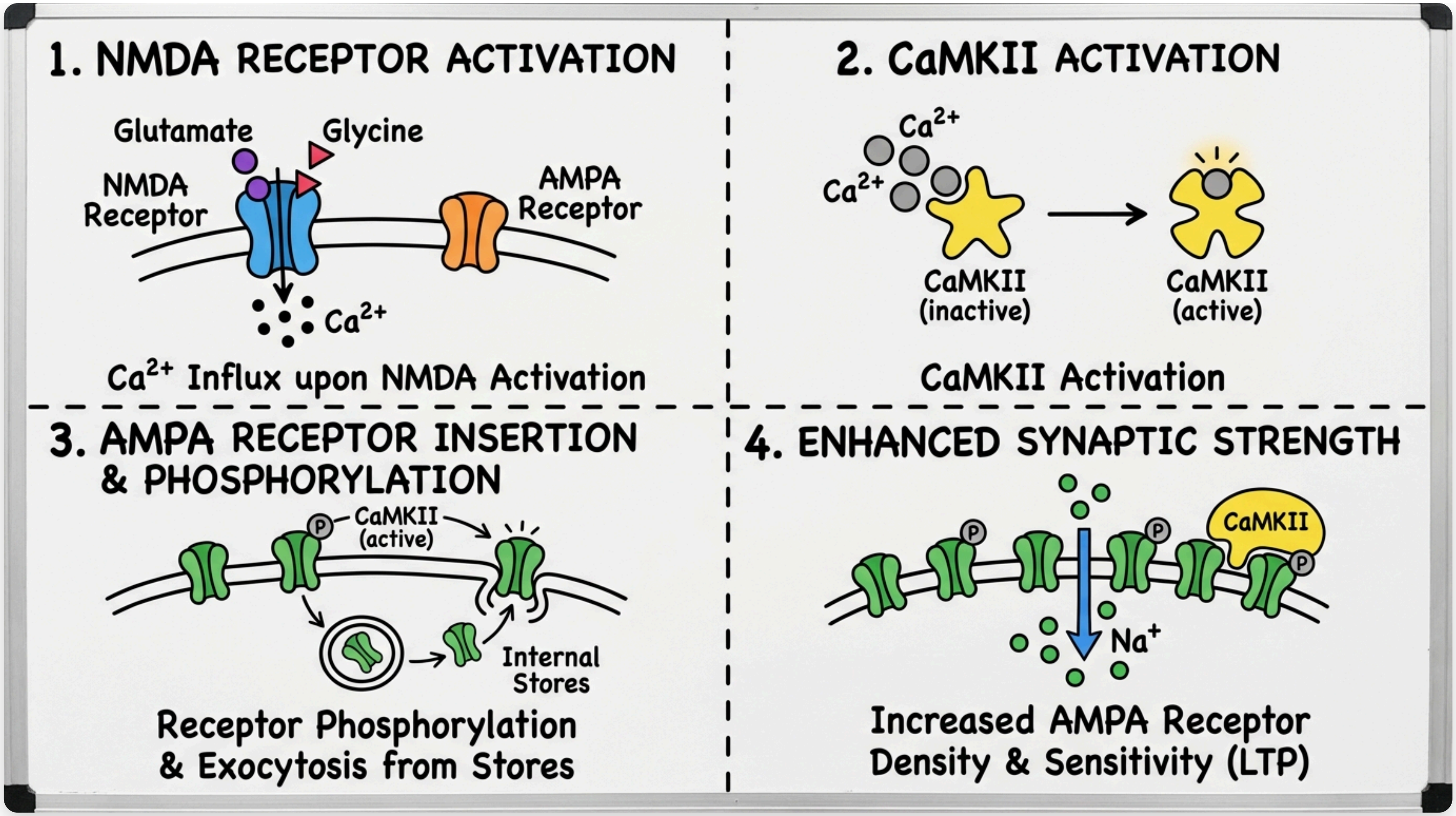
> → Here are 4 main points from the text:
>
> → Postsynaptic spines contain two types of glutamate receptors: AMPA and NMDA.
>
> → AMPA receptors open when glutamate binds, allowing sodium to enter and depolarize the cell.
>
> → NMDA receptors act as molecular coincidence detectors due to a unique blocking mechanism.
>
> → At rest, magnesium blocks the NMDA channel; strong depolarization repels this block, allowing calcium to enter.


PANEL 1: Initial Depolarization
AMPA Receptor
Na+
NMDA Receptor
Glu
Mg2+
Na+
Na+
Resting Potential (-70mV)
Slight Depolarization via AMPA
Slight Depolarization via AMPA
PANEL 2: NMDA Receptor Activation
AMPA Receptor
Na+
NMDA Receptor
Mg2+
Na+
Ca2+
Na+
Strong Depolarization (>-40mV)
Mg2+ block removed by depolarization, Ca2+ influx

AMPA Potentiation

The NMDA Receptor: Nature's Coincidence Detector This calcium is the trigger for everything that follows. It activates calcium/calmodulin-dependent kinase II (CaMKII), which phosphorylates existing AMPA receptors, making them more sensitive. More dramatically, it triggers the insertion of entirely new AMPA receptors into the membrane. Some are pulled from internal stores, others are synthesized on demand. The result is that the same presynaptic release of glutamate now activates more receptors, producing a larger response. The distinction between early-phase LTP, lasting 1-3 hours and requiring only post-translational modifications, and late-phase LTP, requiring new protein synthesis and lasting days to weeks, mirrors the distinction between short-term and long-term memory. Your hippocampus is deciding right now which parts of this lecture deserve protein synthesis.

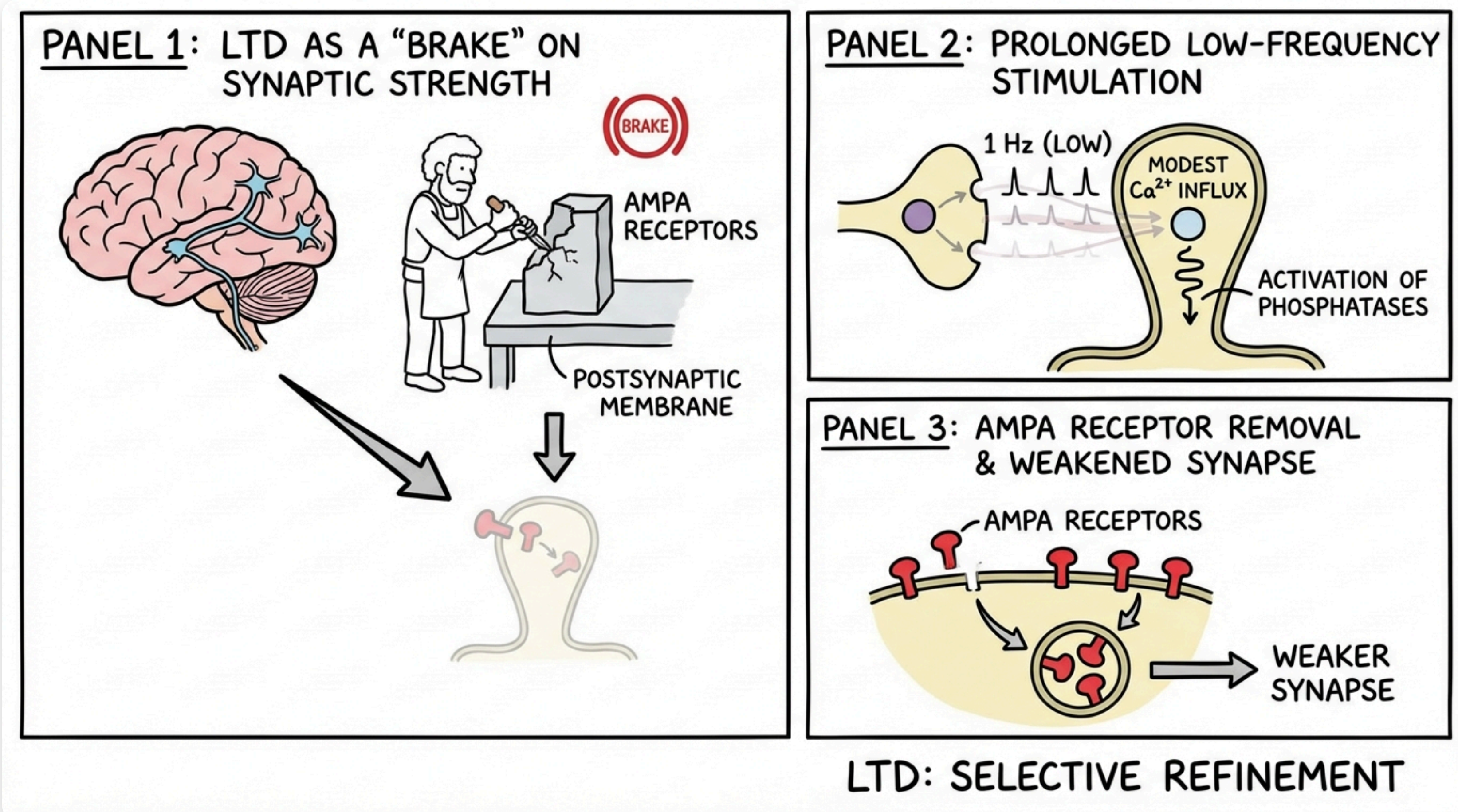
> → Here are 3 main points from the text:
>
> → Calcium triggers changes that make existing receptors more sensitive and add new ones. This results in a stronger response to a signal.
>
> → Early-phase LTP involves changes to existing proteins and lasts hours. Late-phase LTP creates new proteins, lasting for days or weeks.
>
> → Your hippocampus decides which information becomes long-term memory. It does this by triggering the creation of new proteins.


1. NMDA RECEPTOR ACTIVATION
Glutamate
Glycine
NMDA Receptor
AMPA Receptor
Ca2+
Ca2+ Influx upon NMDA Activation
2. CaMKII ACTIVATION
Ca2+
Ca2+
CaMKII (inactive)
CaMKII (active)
CaMKII Activation
3. AMPA RECEPTOR INSERTION & PHOSPHORYLATION
P
CaMKII (active)
Internal Stores
Receptor Phosphorylation & Exocytosis from Stores
4. ENHANCED SYNAPTIC STRENGTH
P
P
CaMKII
P
Na+
Increased AMPA Receptor Density & Sensitivity (LTP)

Long-Term Depression

The NMDA Receptor: Nature's Coincidence Detector Long-Term Depression: The Art of Forgetting If LTP is the accelerator of synaptic strength, long-term depression (LTD) is the brake—and you need both to drive effectively. A synapse that could only strengthen would saturate, losing its ability to encode new information. LTD isn't forgetting; it's selective refinement, the neural equivalent of a sculptor removing excess marble. The induction protocol is LTP's mirror image: instead of brief, high-frequency stimulation, LTD requires prolonged low-frequency stimulation—typically 1 Hz for 15 minutes. This produces a modest calcium influx, enough to activate phosphatases but not kinases. The phosphatases remove phosphate groups from AMPA receptors, making them less sensitive, and trigger the removal of receptors from the membrane entirely.

> - Here are 4 main points from the text:
> - Long-term depression (LTD) acts like a brake for synaptic strength, balancing the strengthening effects of LTP.
> - LTD prevents synapses from becoming oversaturated, allowing them to encode and store new information.
> - Prolonged low-frequency stimulation, such as 1 Hz for 15 minutes, triggers LTD.
> - This stimulation causes a modest calcium influx, activating phosphatases that reduce AMPA receptor sensitivity and remove them from the cell membrane.


PANEL 1: LTD AS A "BRAKE" ON SYNAPTIC STRENGTH
BRAKE
AMPA RECEPTORS
POSTSYNAPTIC MEMBRANE
PANEL 2: PROLONGED LOW-FREQUENCY STIMULATION
1 Hz (LOW)
MODEST Ca^{2+} INFLUX
ACTIVATION OF PHOSPHATASES
PANEL 3: AMPA RECEPTOR REMOVAL & WEAKENED SYNAPSE
AMPA RECEPTORS
WEAKER SYNAPSE
LTD: SELECTIVE REFINEMENT

Cerebellar Motor Learning

The NMDA Receptor: Nature's Coincidence Detector The cerebellum has turned LTD into an art form for motor learning. Every time you make a movement error, climbing fibers from the inferior olive deliver a teaching signal to Purkinje cells, inducing LTD at the parallel fiber synapses that caused the error. This is how you learned to ride a bicycle—by weakening the synapses that produced wobbles and falls.

> - Here are 3-5 main points from the text:
> - The cerebellum uses a process called LTD (long-term depression) to help with motor learning.
> - When you make a movement error, climbing fibers send a teaching signal to brain cells.
> - These teaching signals cause LTD, weakening the synapses linked to the error.
> - Weakening specific synapses helps the brain learn from mistakes and improve motor skills, like riding a bike.

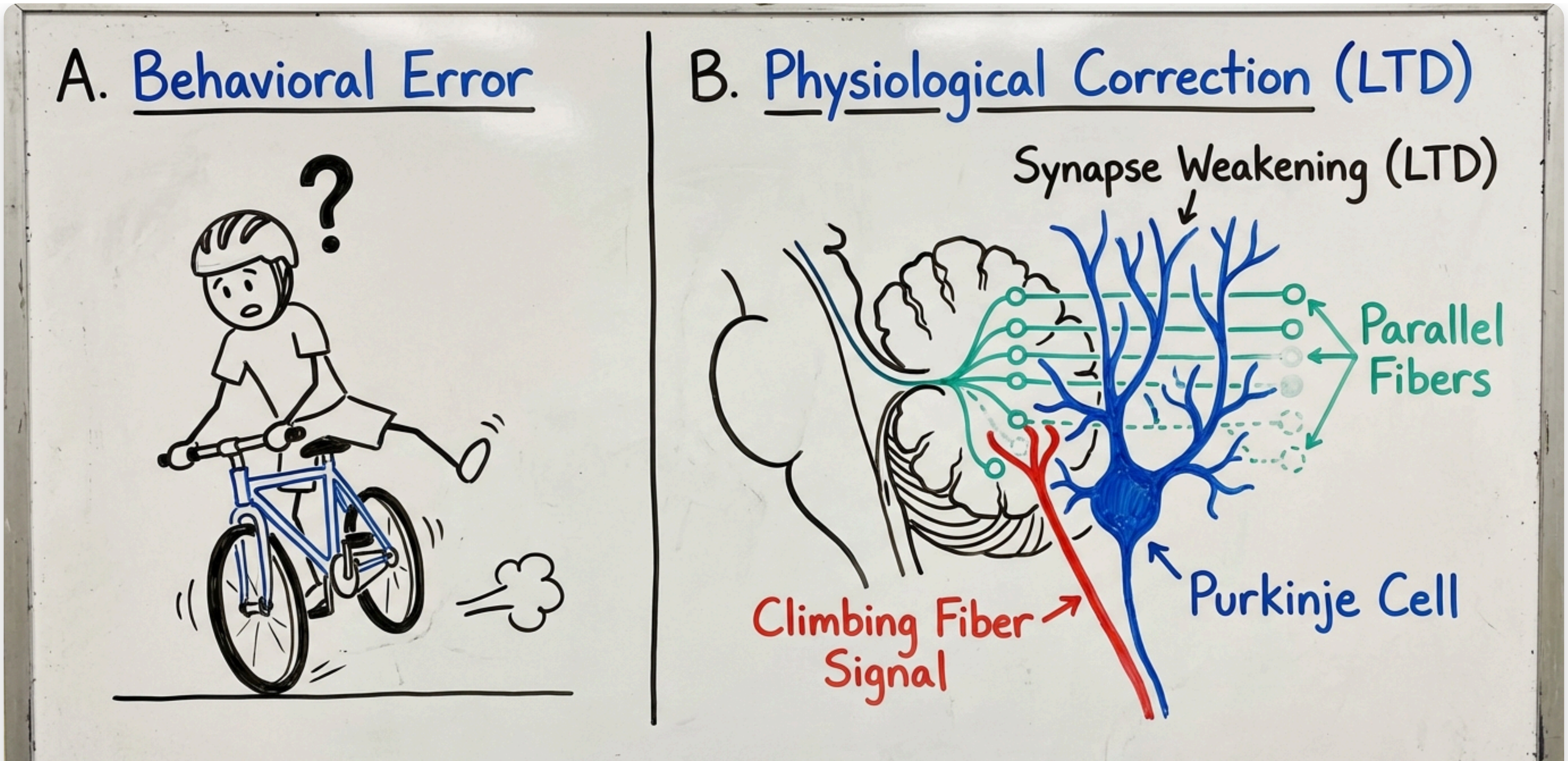
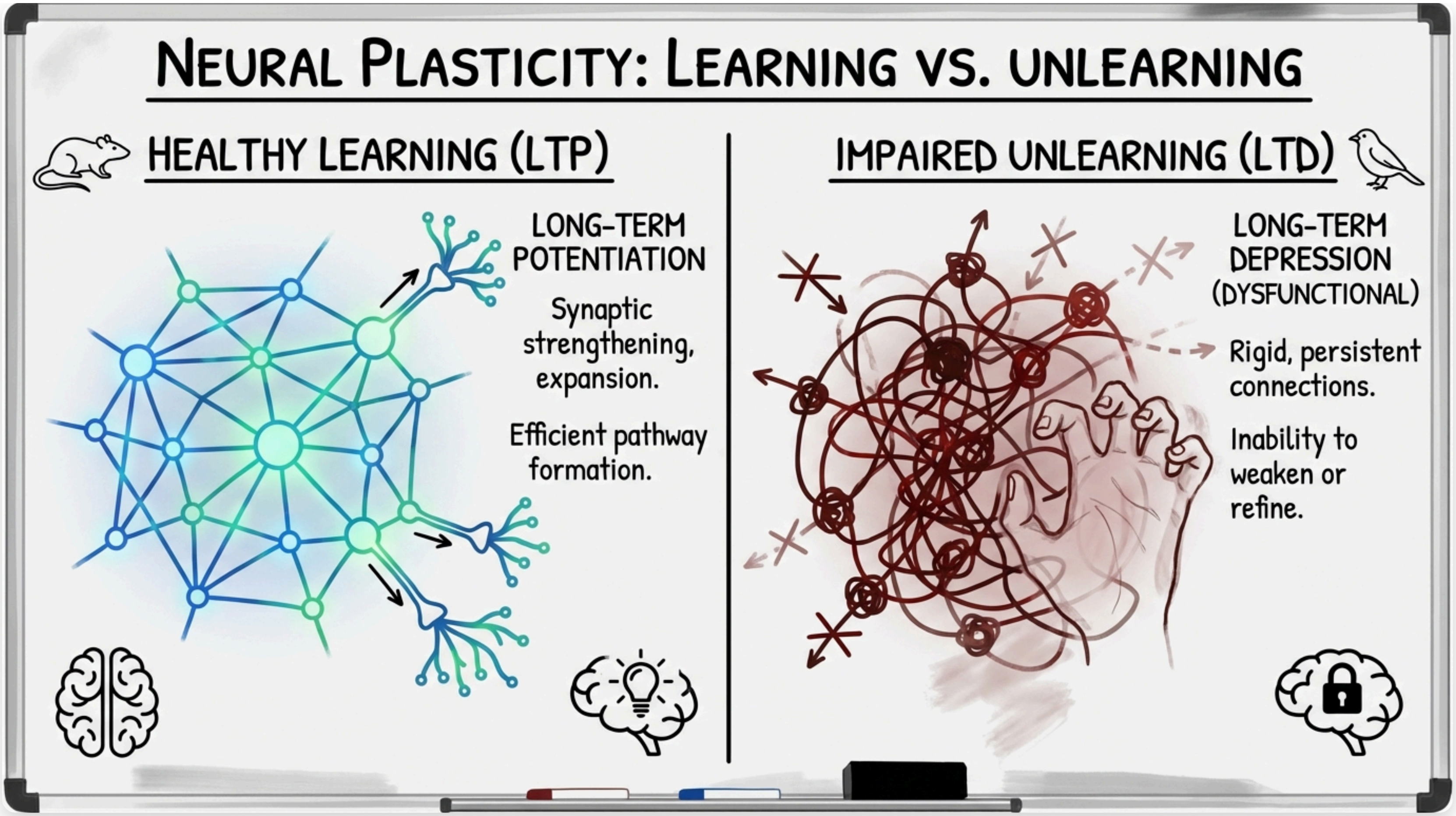


Figure 3.1: Cerebellar error signal leading to long-term depression.

NMDA Receptor Failure

The NMDA Receptor: Nature's Coincidence Detector Let me tell you about Sarah, a composite of several patients I've studied. Sarah was a concert pianist who developed focal dystonia—her fourth and fifth fingers would involuntarily curl when she tried to play scales. The tragedy wasn't just the movement disorder; it was that her brain couldn't unlearn the abnormal pattern. The LTD mechanisms that should have weakened the errant connections were impaired. She could still strengthen synapses through LTP, learning new pieces, but she couldn't erase the pathological motor programs. Her career ended not because she couldn't learn, but because she couldn't forget. This dysfunction in LTD is emerging as a common theme in autism spectrum disorders and schizophrenia. The ability to weaken inappropriate connections is just as important as strengthening appropriate ones. The brain is not just a learning machine—it's a learning and unlearning machine. The Molecular Machinery of Memory Spike-Timing Dependent Plasticity (STDP)

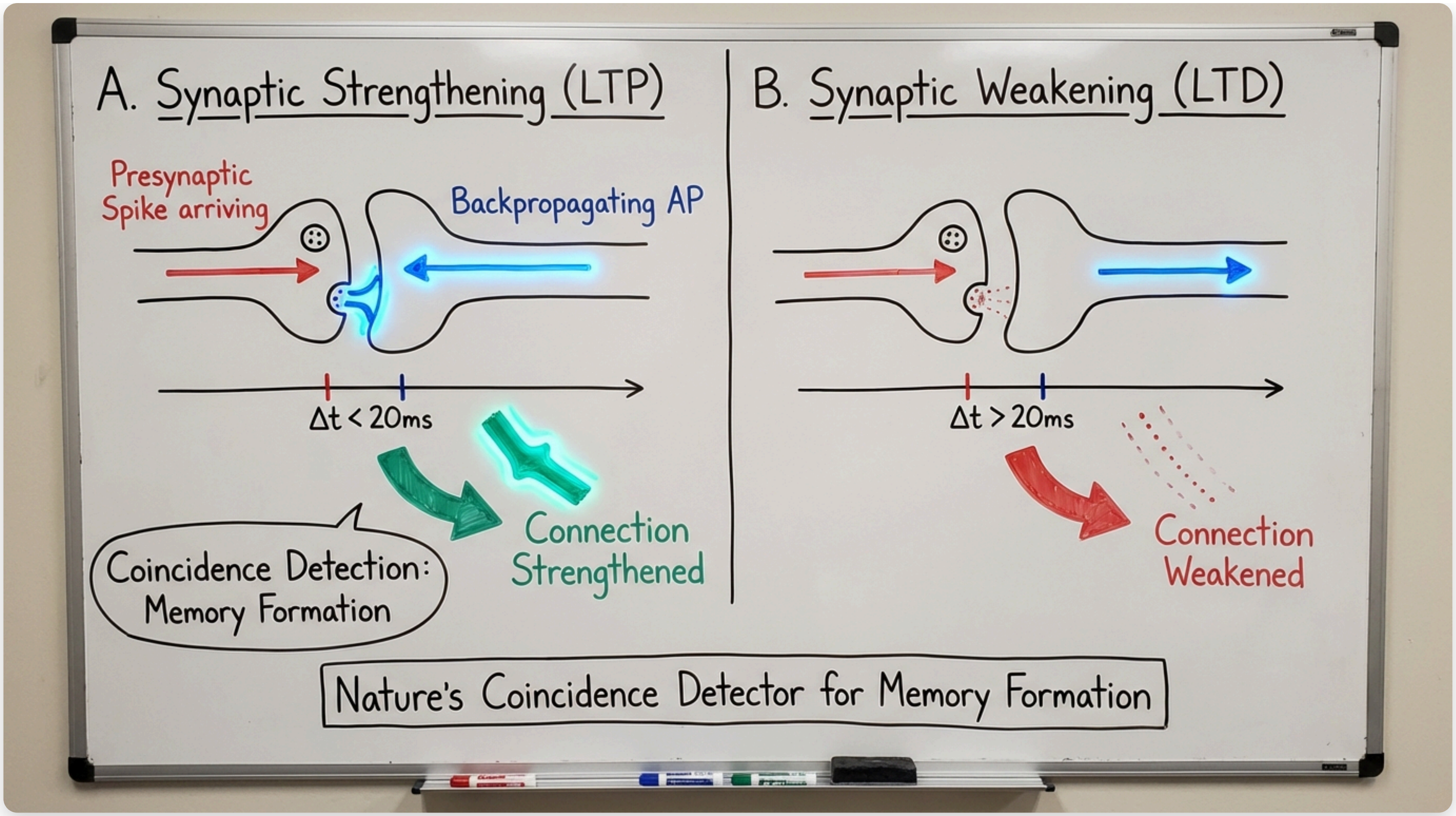
> - Here are 4 main points from the text:
> - Long-Term Depression (LTD) allows the brain to weaken connections it no longer needs.
> - The brain's ability to weaken inappropriate connections is as vital as its ability to strengthen useful ones.
> - Dysfunction in Long-Term Depression (LTD) is a common factor in autism spectrum disorders and schizophrenia.
> - The brain functions as both a learning and an unlearning machine.


NEURAL PLASTICITY: LEARNING VS. UNLEARNING
HEALTHY LEARNING (LTP)
LONG-TERM POTENTIATION
Synaptic strengthening, expansion.
Efficient pathway formation.
IMPAIRED UNLEARNING (LTD)
LONG-TERM DEPRESSION (DYSFUNCTIONAL)
Rigid, persistent connections.
Inability to weaken or refine.

Synaptic Timing

The NMDA Receptor: Nature's Coincidence Detector The brain faces a credit assignment problem: when a neuron fires, which of the thousands of inputs that preceded it should be strengthened? The answer is breathtakingly precise. If a presynaptic spike arrives just before a postsynaptic spike—within 20 milliseconds—that synapse is strengthened. The input is credited with contributing to the output. But if the presynaptic spike arrives just after the postsynaptic spike, the synapse is weakened. The input couldn't have caused the output, so its influence is reduced. This spike-timing dependent plasticity operates on the scale of milliseconds. A difference of 10 milliseconds can determine whether a synapse strengthens or weakens, whether a memory forms or fades. The mechanism involves backpropagating action potentials—when a neuron fires, the signal doesn't just go forward down the axon, it also propagates backward into the dendrites, announcing to all synapses: "The cell just fired."

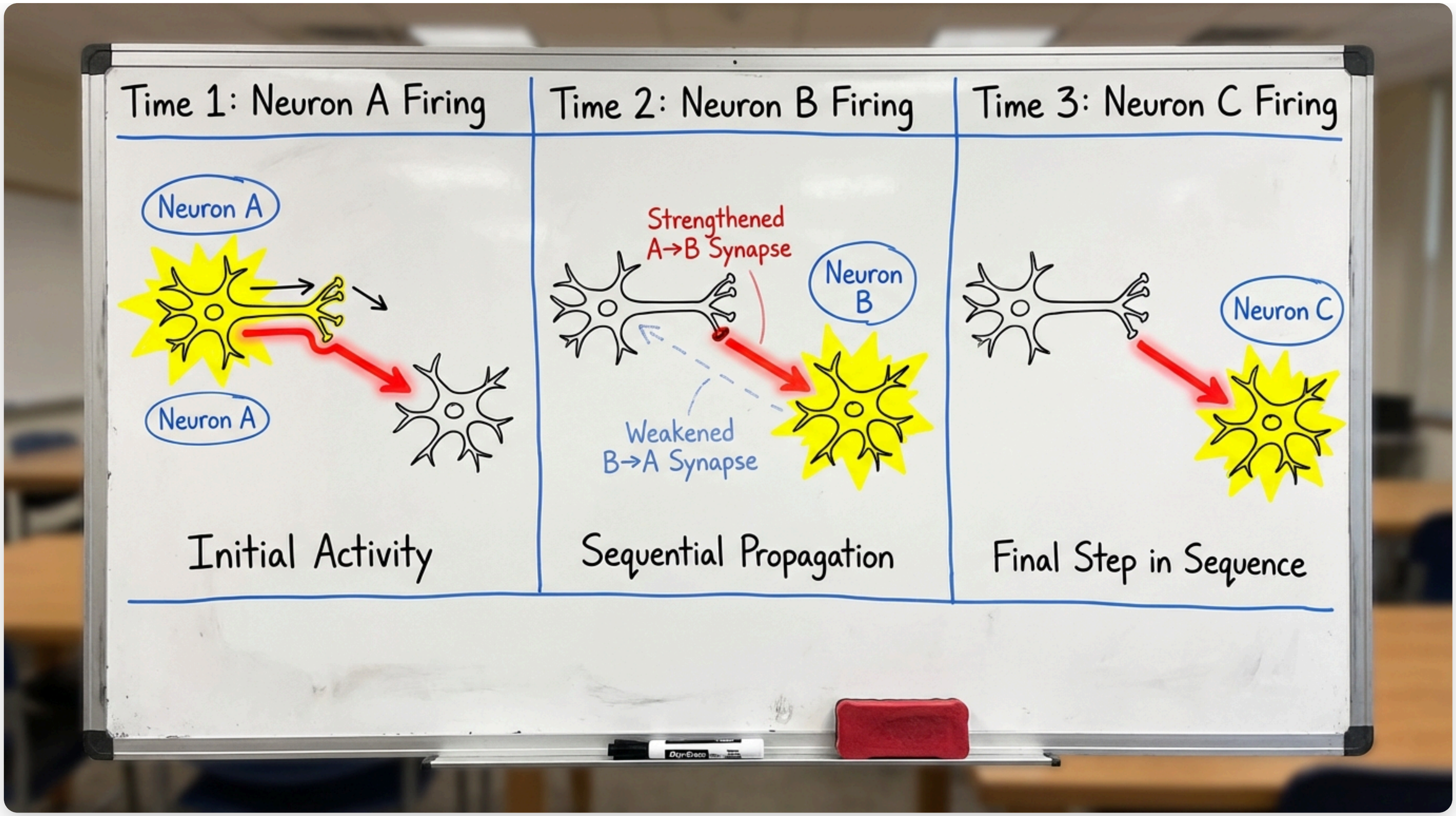
> → Here are 4 main points from the text:
>
> → Synapses in the brain strengthen or weaken depending on the exact timing of electrical signals.
>
> → A synapse strengthens when an incoming signal arrives just before the neuron fires, and it weakens when the signal arrives just after.
>
> → This rapid process, called spike-timing dependent plasticity, uses millisecond differences to influence whether memories form or fade.
>
> → When a neuron fires, it sends signals backward to its dendrites, telling all its synapses that it has just fired.


A. Synaptic Strengthening (LTP)
B. Synaptic Weakening (LTD)
Presynaptic
Spike arriving
Backpropagating AP
Δt < 20ms
Δt > 20ms
Coincidence Detection:
Memory Formation
Connection
Strengthened
Connection
Weakened
Nature's Coincidence Detector for Memory Formation

NMDA Sequence Learning

The NMDA Receptor: Nature's Coincidence Detector This timing window explains how you learn sequences. When you memorized your phone number, neurons representing each digit fired in sequence. The synapse from the "5" neuron to the "5" neuron was strengthened because "5" consistently fired just before "5." The reverse connections were weakened. The sequence became encoded in the asymmetric pattern of synaptic strengths.

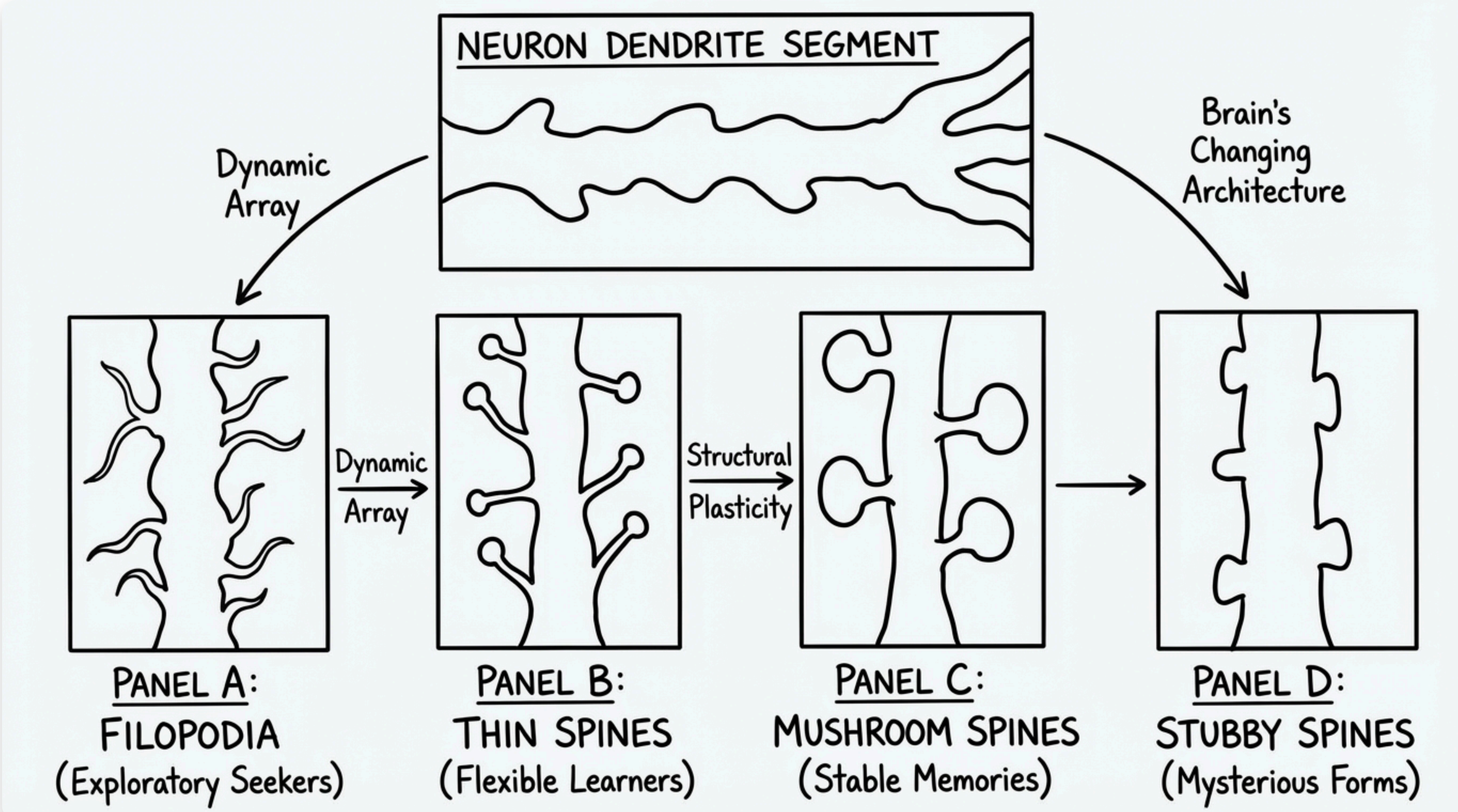
> - Here are 3 main points from the text:
> - The NMDA receptor helps the brain learn sequences by detecting when neurons fire together in a specific order.
> - Neurons strengthen their connections when they consistently fire one after another in a specific sequence.
> - The brain encodes learned sequences as an asymmetric pattern of strong synaptic connections.


Time 1: Neuron A Firing
Time 2: Neuron B Firing
Time 3: Neuron C Firing
Neuron A
Neuron A
Strengthened
A→B Synapse
Neuron
B
Weakened
B→A Synapse
Neuron C
Initial Activity
Sequential Propagation
Final Step in Sequence

Structural Plasticity

Structural Plasticity: The Shapeshifters We've been talking about functional changes—the same structures working differently. But the brain also undergoes structural plasticity—the physical architecture itself changes. Dendritic spines, those tiny protrusions where excitatory synapses form, are the most dynamic structures in your brain. Spines come in distinct flavors, each with different functions. Filopodia are the seekers—thin, highly motile projections that sample the environment for new synaptic partners, extending and retracting over minutes. Thin spines are the learners—flexible structures with small heads that can rapidly strengthen or weaken based on activity. Mushroom spines are the memories—large, stable structures with big heads that can persist for months or years. Stubby spines remain mysterious, neither clearly learning nor remembering, possibly serving as a reserve pool.

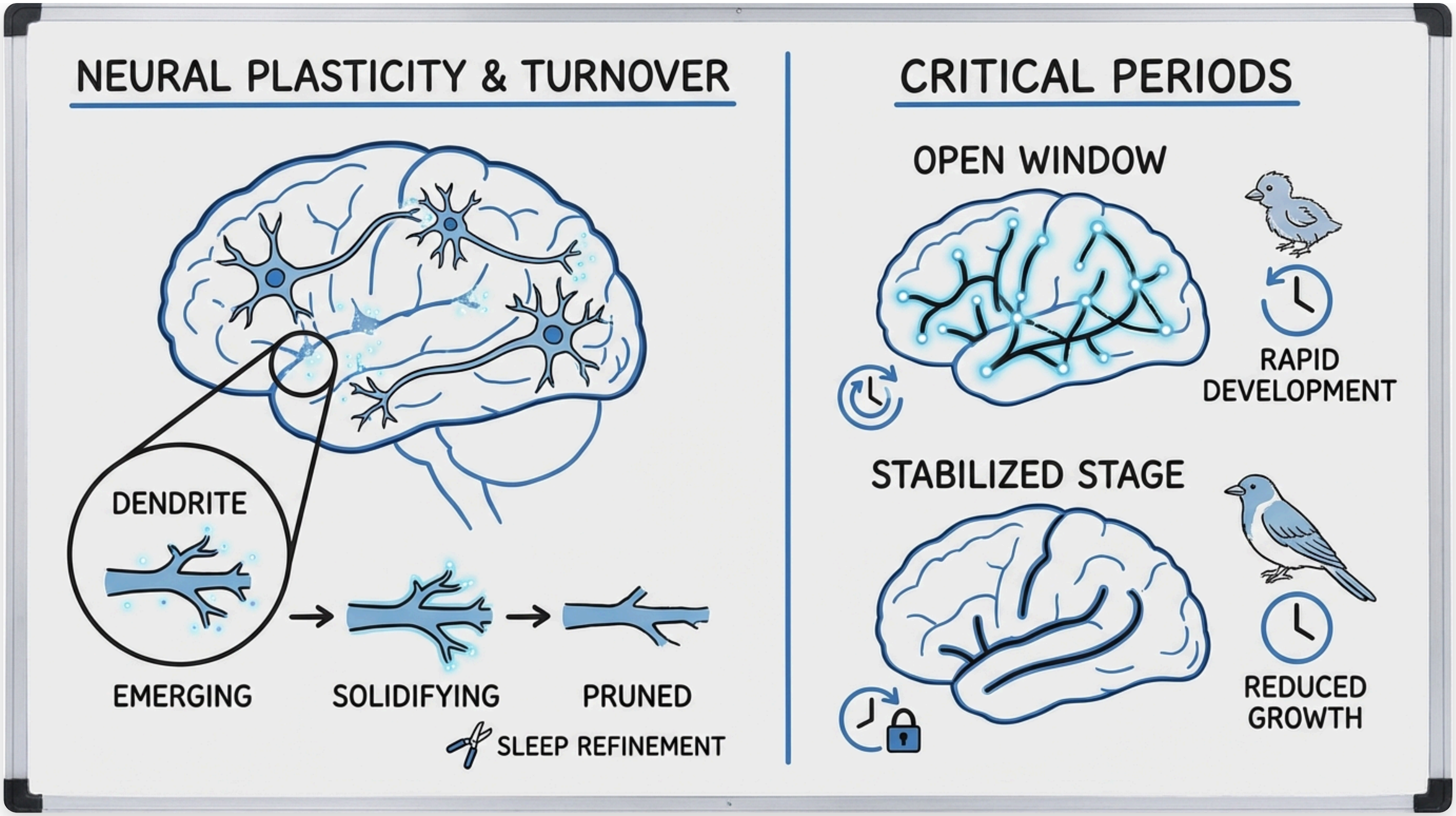
- Main Points:
- Structural plasticity means the brain's physical architecture changes.
- Dendritic spines are dynamic structures in the brain where connections form.
- Filopodia are seeker spines that actively look for new connections.
- Thin spines help the brain learn quickly, and mushroom spines store long-term memories.


NEURON DENDRITE SEGMENT
Dynamic
Array
Brain's
Changing
Architecture
Dynamic
Array
Structural
Plasticity
PANEL A:
FILOPODIA
(Exploratory Seekers)
PANEL B:
THIN SPINES
(Flexible Learners)
PANEL C:
MUSHROOM SPINES
(Stable Memories)
PANEL D:
STUBBY SPINES
(Mysterious Forms)

Structural Plasticity

Structural Plasticity: The Shapeshifters Two-photon microscopy has revealed a truth that would have stunned Cajal: spines appear and disappear in living brains over hours. In motor cortex during skill learning, 10-15% of spines turn over daily. During sleep, weak spines are selectively eliminated while strong ones are preserved—your brain literally prunes connections while you dream. This is why sleep deprivation impairs memory; without pruning, the signal-to-noise ratio deteriorates. Critical Periods: Windows of Opportunity Hubel and Wiesel's Kittens David Hubel and Torsten Wiesel's experiments in the 1960s were elegant in design and troubling in implication. They sutured one eye closed in newborn kittens, then examined the visual cortex weeks later. What they found revolutionized neuroscience: neurons that should have responded to both eyes now responded only to the eye that had remained open. The deprived eye hadn't gone blind—the retina was fine—but the cortical territory had been conquered by the experienced eye.

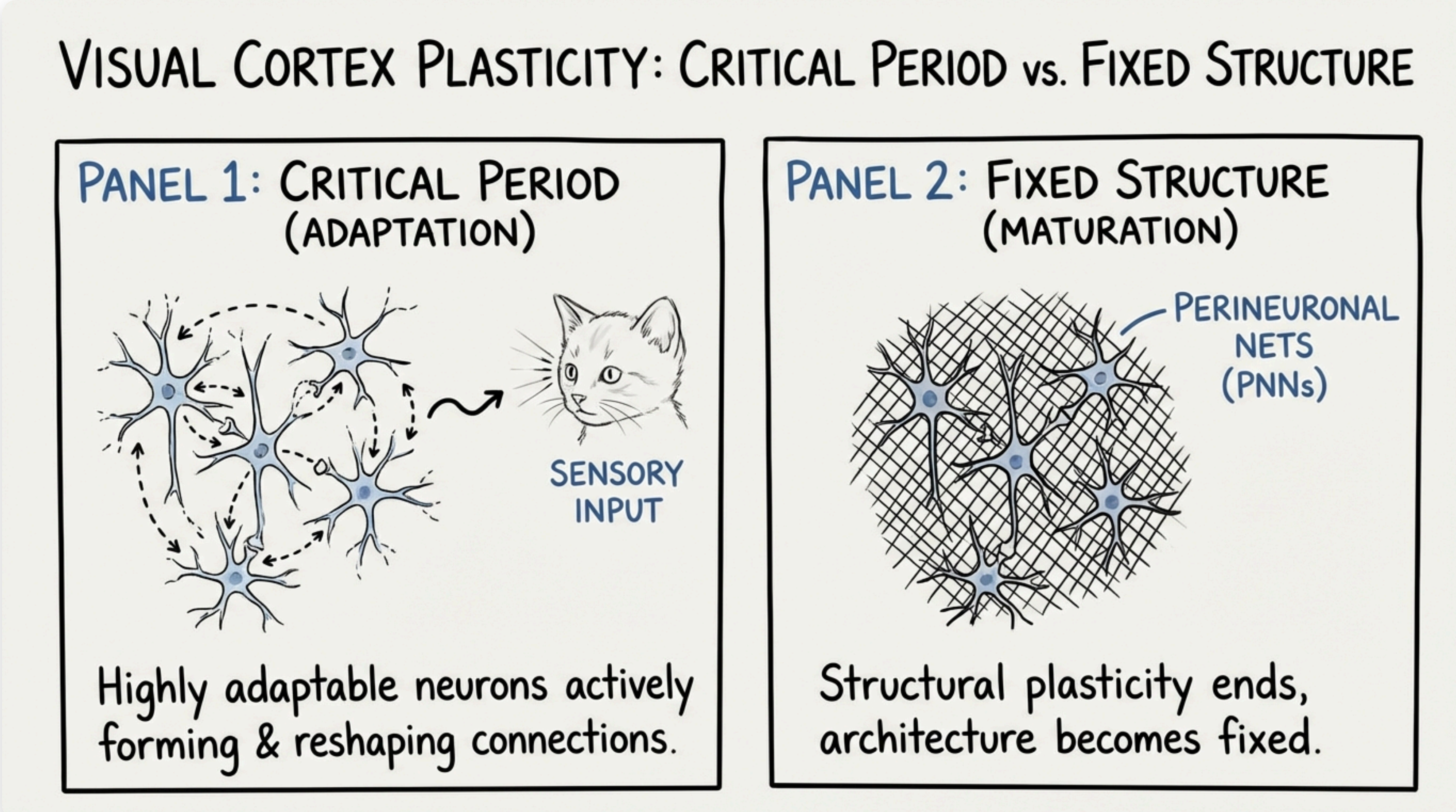
> - Here are 3 main points from the text:
> - Brain connections called spines continuously appear and disappear in living brains, especially when learning new skills.
> - During sleep, the brain strengthens important connections and eliminates weak ones. This process helps to improve memory.
> - Experiments show that early life experiences significantly and permanently shape brain development, such as how visual pathways form.


NEURAL PLASTICITY & TURNOVER
DENDRITE
EMERGING
SOLIDIFYING
PRUNED
SLEEP REFINEMENT
CRITICAL PERIODS
OPEN WINDOW
RAPID DEVELOPMENT
STABILIZED STAGE
REDUCED GROWTH

Visual Critical Plasticity

Structural Plasticity: The Shapeshifters The crucial discovery was timing. The same deprivation in adult cats had minimal effect. There was a critical period, from about 3 weeks to 3 months in cats, when visual experience literally shaped the physical architecture of visual cortex. Miss this window, and the organization became permanent. In humans, this critical period extends to about age seven. Children with cataracts or strabismus (crossed eyes) must be treated early or face permanent amblyopia—"lazy eye"—not because the eye is lazy, but because the brain has reassigned its territory. The molecular brake that ends this period involves perineuronal nets—specialized extracellular matrix structures that literally cage neurons, restricting structural plasticity.

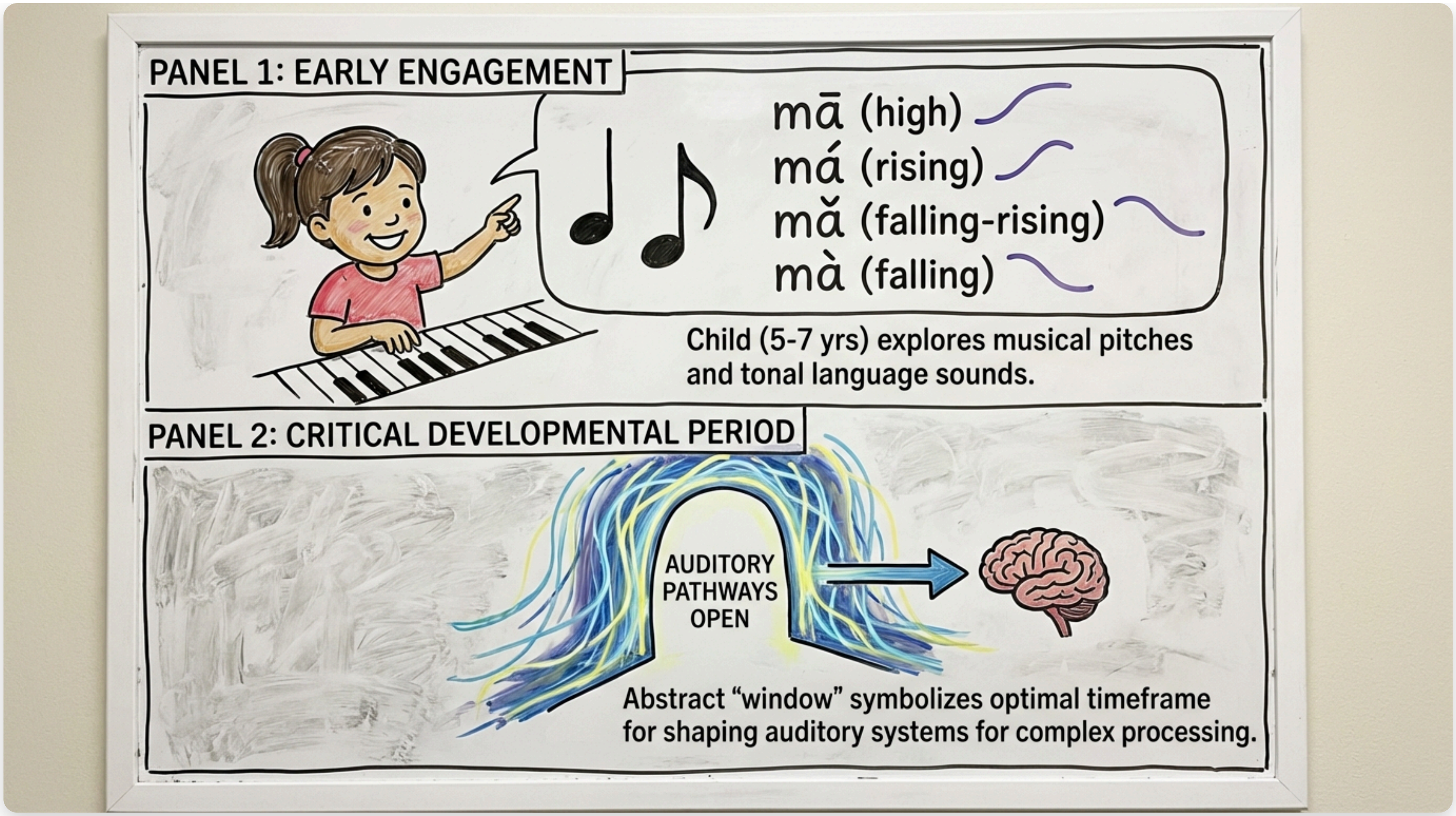
> → Main Points:
>
> → Visual experience during a critical period physically shapes the brain's visual architecture.
>
> → This critical period lasts until about age seven in humans.
>
> → Untreated eye problems in children during this time can cause permanent "lazy eye" because the brain reassigns its visual territory.
>
> → Specialized perineuronal nets end the critical period by caging neurons.


VISUAL CORTEX PLASTICITY: CRITICAL PERIOD vs. FIXED STRUCTURE
PANEL 1: CRITICAL PERIOD (ADAPTATION)
SENSORY INPUT
Highly adaptable neurons actively forming & reshaping connections.
PANEL 2: FIXED STRUCTURE (MATURATION)
PERINEURONAL NETS (PNNs)
Structural plasticity ends, architecture becomes fixed.

Ability Critical Periods

Language and Perfect Pitch The story of Genie haunts neuroscience. Discovered in 1970 at age 13, she had been locked in isolation since 20 months old, never spoken to, never taught language. Despite intensive therapy, she never developed normal language abilities. Her tragedy demonstrated that human language has a critical period—miss it, and the capacity is permanently diminished. Perfect pitch provides a more benign window into critical periods. Children who begin musical training before age seven are far more likely to develop absolute pitch—the ability to identify or produce notes without a reference. But here's the fascinating part: speakers of tonal languages like Mandarin, where pitch carries meaning, are nine times more likely to have perfect pitch. Their language experience during the critical period tunes their auditory system differently.

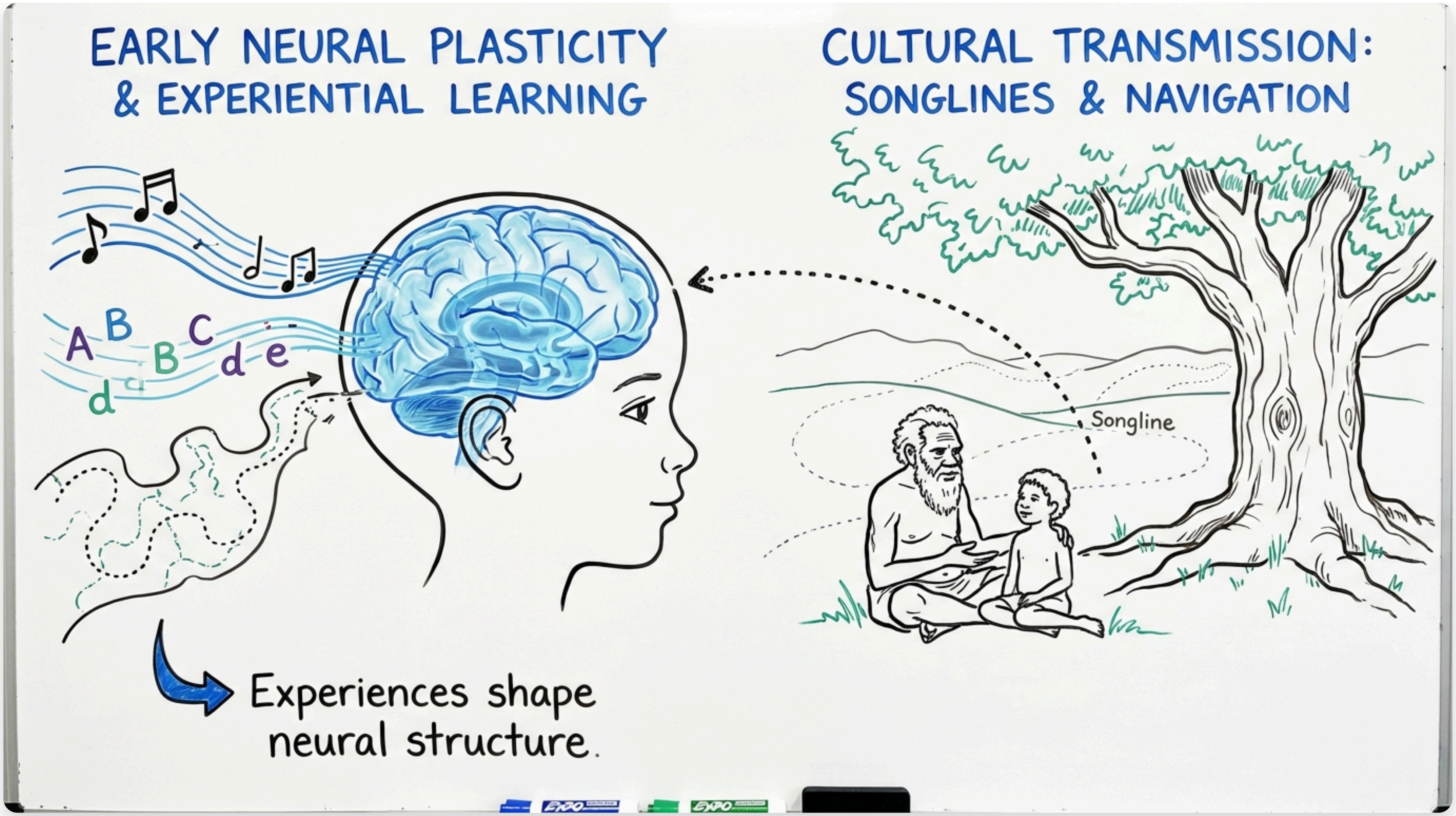
> - Here are 3 main points from the text:
> - Humans have a critical period for learning language. Missing this period permanently diminishes one's ability to develop normal language skills.
> - Children who begin musical training before age seven are more likely to develop perfect pitch.
> - Speakers of tonal languages like Mandarin are much more likely to have perfect pitch. Their early language experience tunes their auditory system differently.


PANEL 1: EARLY ENGAGEMENT
mā (high)
má (rising)
mǎ (falling-rising)
mà (falling)
Child (5-7 yrs) explores musical pitches and tonal language sounds.
PANEL 2: CRITICAL DEVELOPMENTAL PERIOD
AUDITORY PATHWAYS OPEN
Abstract “window” symbolizes optimal timeframe for shaping auditory systems for complex processing.

Auditory Brain Shaping

Language and Perfect Pitch Think about what this means. The language you heard as a baby literally shaped how your brain processes sound. The music you heard before age seven influenced whether you can ever have perfect pitch. These aren't just memories—they're architectural changes that last a lifetime. Indigenous Australian cultures use songlines—musical maps of the landscape—to navigate thousands of miles of territory. Children learn these songs during the critical period for both language and spatial navigation, creating neural representations that integrate music, language, and space in ways that would be impossible to achieve as an adult. Their brains are literally organized differently because of childhood experience.

> → Here are 4 main points from the text:
>
> → The language a baby hears physically shapes how their brain processes sounds.
>
> → Music heard before age seven influences a person's ability to develop perfect pitch.
>
> → Early childhood experiences create lasting, physical changes in the brain's structure.
>
> → Children who learn songlines integrate music, language, and space in their brains. This experience permanently organizes their brains differently.

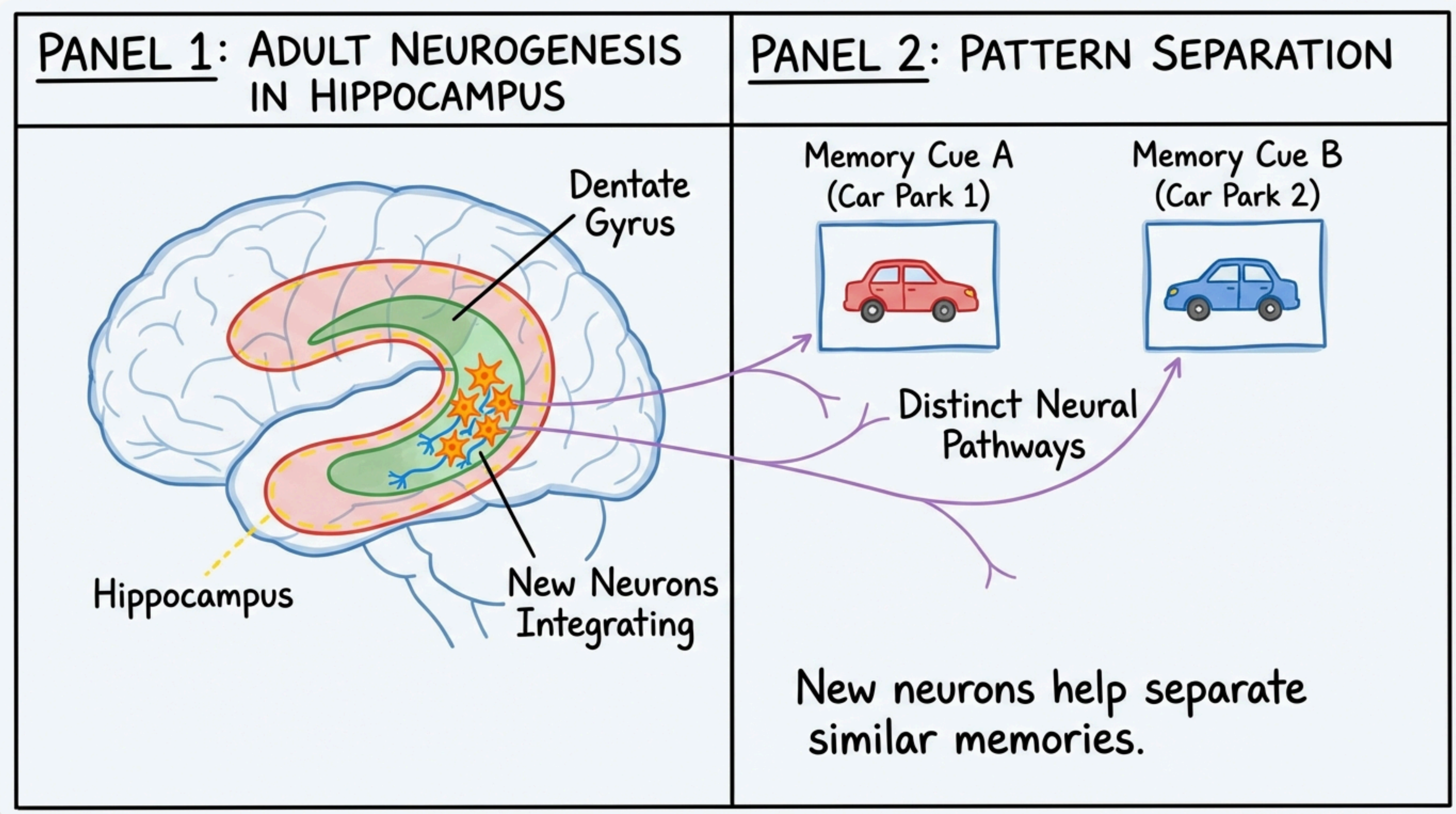


EARLY NEURAL PLASTICITY & EXPERIENTIAL LEARNING
CULTURAL TRANSMISSION: SONGLINES & NAVIGATION
A B B C d e
d
Songline
Experiences shape neural structure.

Adult Neurogenesis

Language and Perfect Pitch Adult Neurogenesis: The Brain That Keeps Growing For most of the 20th century, neuroscience dogma held that adult brains don't generate new neurons. Santiago Ramón y Cajal himself wrote, "In adult centers, the nerve paths are something fixed, ended, immutable." This dogma died in the 1990s when researchers discovered that the adult human brain produces about 2000 new neurons every day in the dentate gyrus of the hippocampus. These aren't replacement neurons filling in for dead cells—they're additional neurons integrating into existing circuits. Young adult neurons have unique properties: they're more excitable, more plastic, and particularly good at pattern separation—distinguishing between similar memories. When you remember where you parked today versus yesterday, newly born neurons help keep those similar memories distinct.

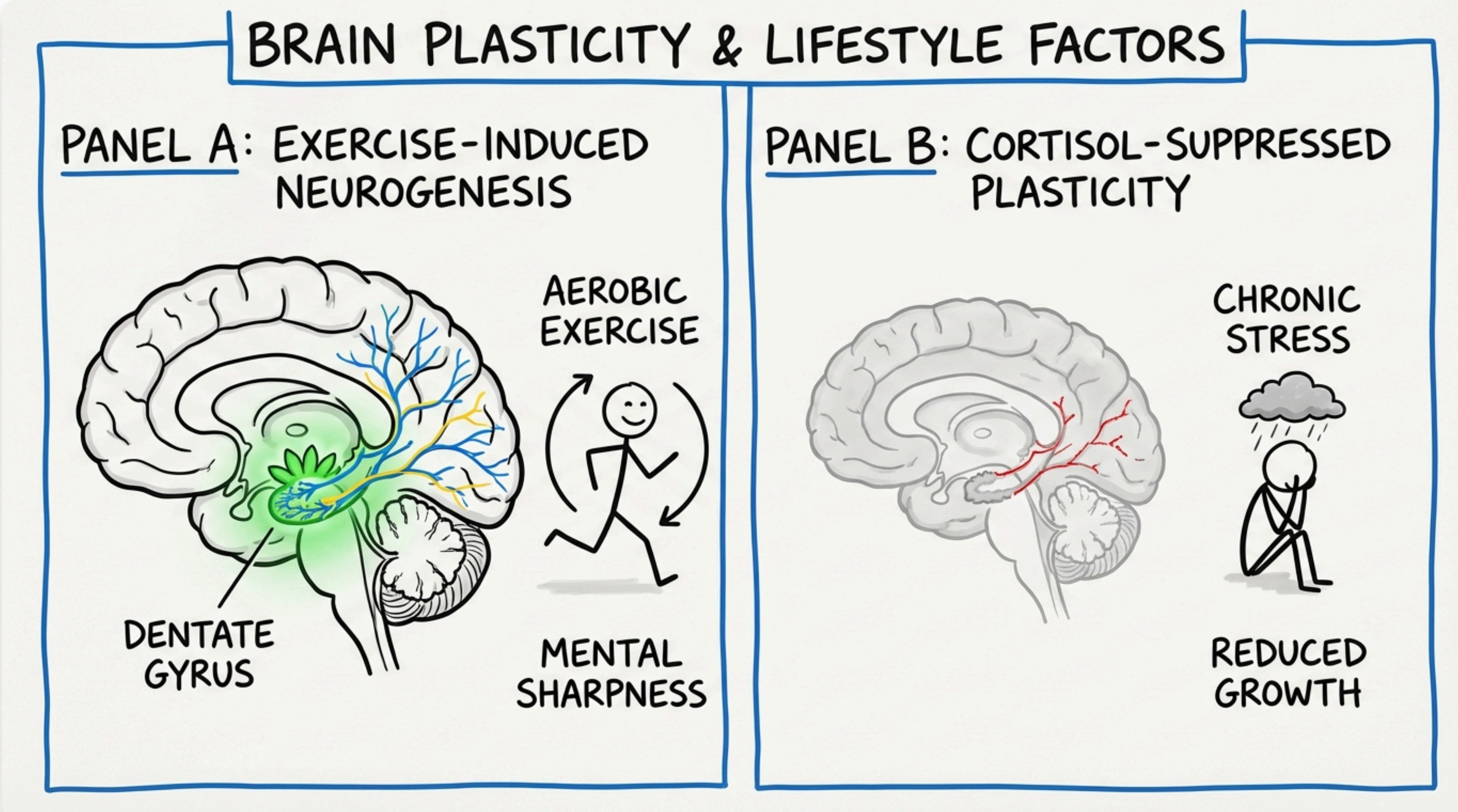
> → Main Points:
>
> → The adult human brain creates about 2,000 new neurons every day.
>
> → These new neurons develop in the hippocampus and add to the brain's existing circuits.
>
> → New adult neurons are more excitable, more adaptable, and help distinguish between similar memories.


PANEL 1: ADULT NEUROGENESIS IN HIPPOCAMPUS
Dentate Gyrus
Hippocampus
New Neurons Integrating
PANEL 2: PATTERN SEPARATION
Memory Cue A (Car Park 1)
Memory Cue B (Car Park 2)
Distinct Neural Pathways
New neurons help separate similar memories.

Exercise Neurogenesis

Language and Perfect Pitch Physical exercise doubles the rate of neurogenesis. When mice run on wheels, their dentate gyrus blooms with new neurons. This isn't just correlation—the new neurons are necessary for the cognitive benefits of exercise. Block neurogenesis pharmacologically, and exercise no longer improves memory. This is why that morning run makes you mentally sharper—you're literally growing new brain cells. Chronic stress has the opposite effect. Cortisol, the stress hormone, suppresses neurogenesis almost completely. This creates a vicious cycle: stress impairs memory, which creates more stress, which further suppresses neurogenesis. Depression is associated with reduced hippocampal volume, partly due to decreased neurogenesis. Many antidepressants, including SSRIs, work in part by restoring neurogenesis—they don't just change chemical balances, they restart brain growth.

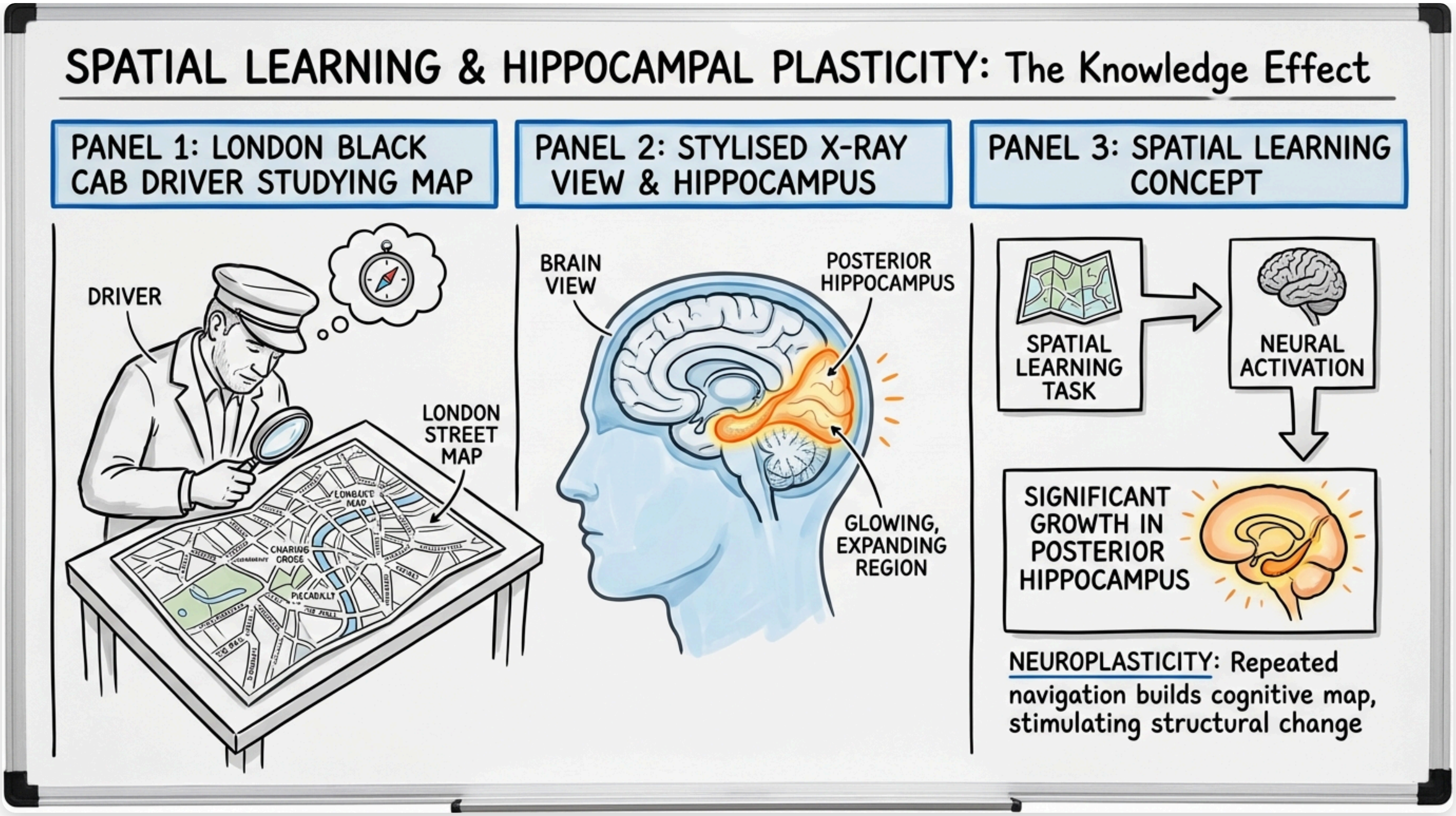
> - Here are 3 main points from the text:
> - Regular exercise helps your brain grow new cells. These new cells make your mind sharper and improve your memory.
> - Long-term stress reduces the growth of new brain cells. This damages memory and can create more stress.
> - Many antidepressant medications help new brain cells grow again. This process aids in treating conditions like depression.


BRAIN PLASTICITY & LIFESTYLE FACTORS
PANEL A: EXERCISE-INDUCED NEUROGENESIS
AEROBIC EXERCISE
DENTATE GYRUS
MENTAL SHARPNESS
PANEL B: CORTISOL-SUPPRESSED PLASTICITY
CHRONIC STRESS
REDUCED GROWTH

London Taxi Brain

The London Taxi Driver Study The famous London taxi driver study revealed that spatial learning physically changes brain structure. Trainee drivers studying "The Knowledge"—London's 25,000 streets—show progressive growth of posterior hippocampus over their 3-4 year training. The volume increase correlates with navigation performance. Their brains literally expand to accommodate the map of London. Even brief interventions can trigger structural changes. Eight weeks of mindfulness meditation increases gray matter density in hippocampus and decreases it in amygdala—growing memory while shrinking fear. Two weeks of juggling training increases gray matter in visual motion areas. Your brain is constantly remodeling based on what you ask it to do.

> → Here are 4 main points from the text:
>
> → Learning complex navigation, like driving a London taxi, causes a specific part of the brain to grow.
>
> → Your brain constantly changes and reshapes itself based on the activities you do.
>
> → Practicing mindfulness meditation can increase brain areas related to memory and decrease areas linked to fear.
>
> → Even brief training, such as juggling, increases brain matter in areas that process visual movement.

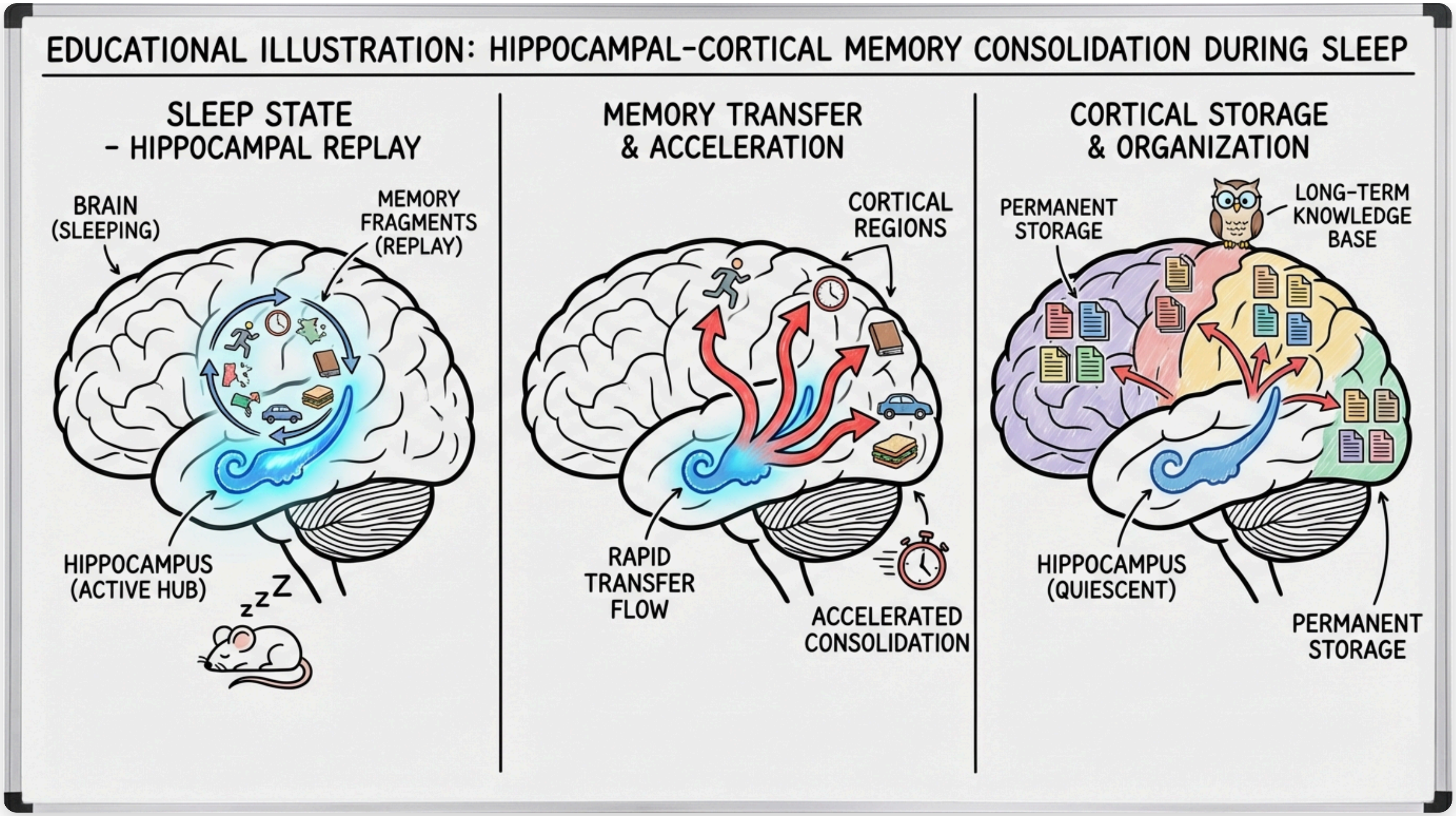


SPATIAL LEARNING & HIPPOCAMPAL PLASTICITY: The Knowledge Effect
PANEL 1: LONDON BLACK CAB DRIVER STUDYING MAP
PANEL 2: STYLISED X-RAY VIEW & HIPPOCAMPUS
PANEL 3: SPATIAL LEARNING CONCEPT
DRIVER
LONDON STREET MAP
CHARING CROSS
PICCADILLY
BRAIN VIEW
POSTERIOR HIPPOCAMPUS
GLOWING, EXPANDING REGION
SPATIAL LEARNING TASK
NEURAL ACTIVATION
SIGNIFICANT GROWTH IN POSTERIOR HIPPOCAMPUS
NEUROPLASTICITY: Repeated navigation builds cognitive map, stimulating structural change

Memory Consolidation

The London Taxi Driver Study Memory Consolidation: From Hippocampus to Cortex The memories forming in your hippocampus right now face a journey. If deemed important, they'll gradually transfer to cortex through systems consolidation—a process that can take years. The hippocampus is like a temporary holding area, keeping memories until cortex is ready to store them permanently. During sleep, your brain replays the day's experiences at high speed. Sharp-wave ripples in the hippocampus—brief bursts at 150-250 Hz—compress hours of experience into seconds of replay. Place cells that fired in sequence as you walked through campus today will fire in the same sequence tonight, but accelerated 20-fold. This replay drives the gradual transfer to cortical storage.

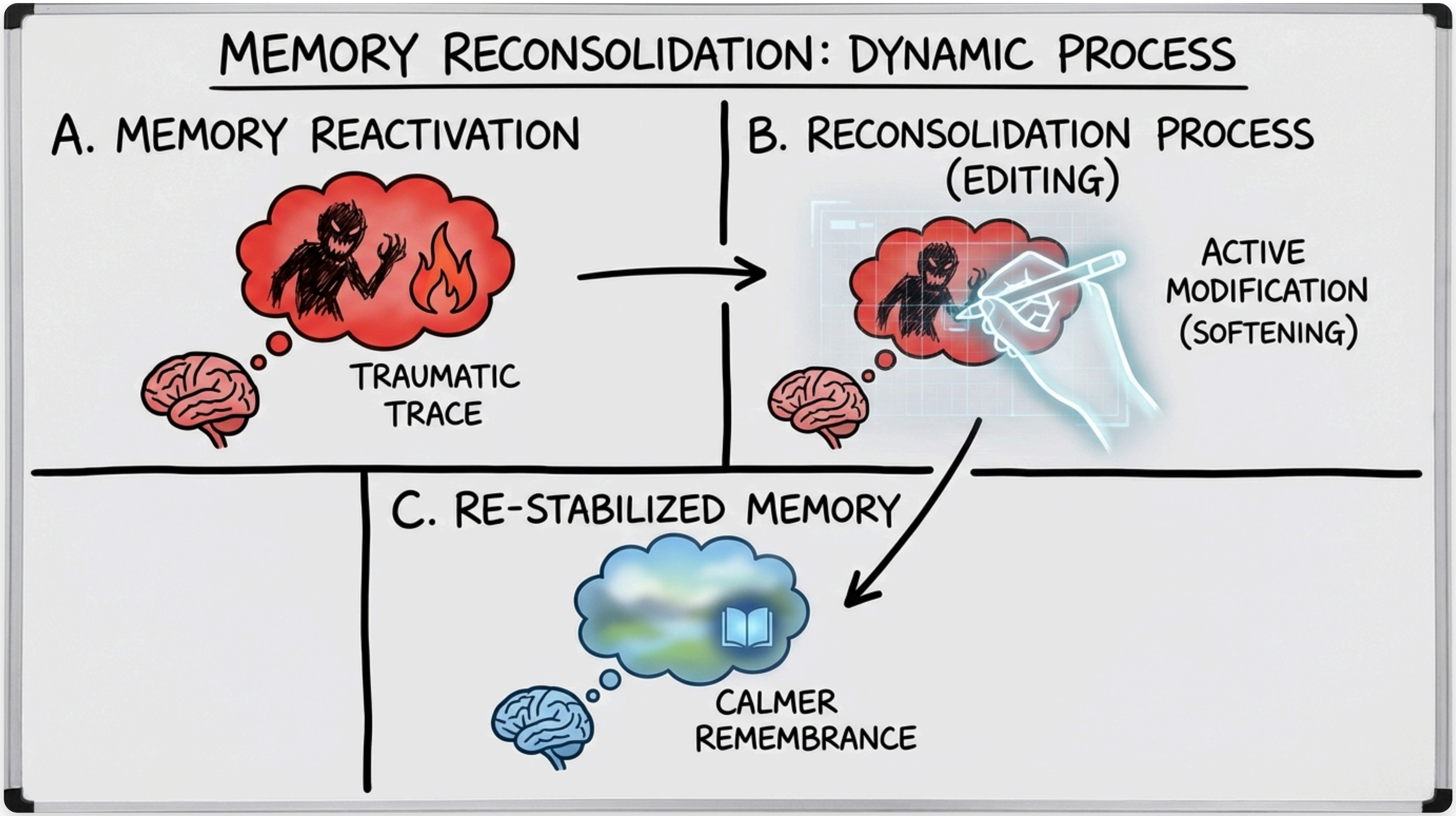
> - Memories first form in the hippocampus and then transfer to the cortex for long-term storage.
> - The hippocampus serves as a temporary holding area for new memories.
> - During sleep, your brain quickly replays the day's experiences.
> - This rapid replay helps move memories from the hippocampus to the cortex for permanent storage.


EDUCATIONAL ILLUSTRATION: HIPPOCAMPAL-CORTICAL MEMORY CONSOLIDATION DURING SLEEP
SLEEP STATE - HIPPOCAMPAL REPLAY
BRAIN (SLEEPING)
MEMORY FRAGMENTS (REPLAY)
HIPPOCAMPUS (ACTIVE HUB)
zzZ
MEMORY TRANSFER & ACCELERATION
CORTICAL REGIONS
RAPID TRANSFER FLOW
ACCELERATED CONSOLIDATION
CORTICAL STORAGE & ORGANIZATION
PERMANENT STORAGE
LONG-TERM KNOWLEDGE BASE
HIPPOCAMPUS (QUIESCENT)
PERMANENT STORAGE

Memory Rewriting

The London Taxi Driver Study Here's the twist that explains why eyewitness testimony is unreliable: reconsolidation. When you recall a memory, it becomes temporarily labile again, requiring new protein synthesis to restabilize. During this window, the memory can be modified, updated, or even erased. Every time you remember something, you literally re-write it. The memory of your first kiss isn't from your first kiss—it's from the last time you remembered it. This has therapeutic implications. Propranolol, a beta-blocker, can weaken traumatic memories if given during recall. PTSD patients who take propranolol while recounting trauma show reduced fear responses in future recalls. We're not erasing memories—we're editing their emotional weight during reconsolidation.

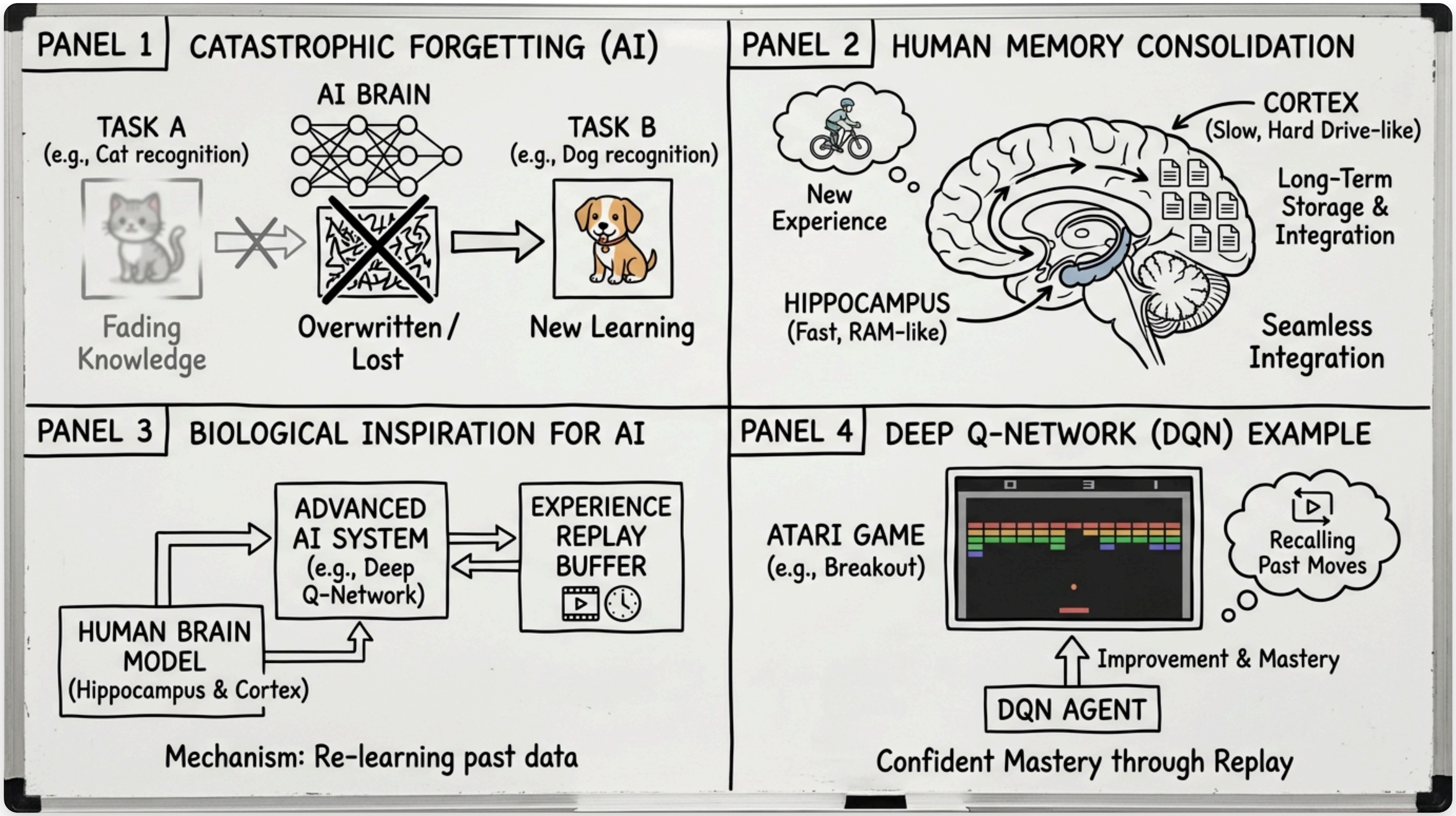
> → Main Points:
>
> → Recalling a memory makes it temporarily unstable and open to change.
>
> → Every time you remember something, you effectively rewrite that memory.
>
> → A drug called Propranolol can weaken traumatic memories.
>
> → Patients take Propranolol during memory recall to reduce the fear linked to the memory.


MEMORY RECONSOLIDATION: DYNAMIC PROCESS
A. MEMORY REACTIVATION
TRAUMATIC TRACE
B. RECONSOLIDATION PROCESS (EDITING)
ACTIVE MODIFICATION (SOFTENING)
C. RE-STABILIZED MEMORY
CALMER REMEMBRANCE

Catastrophic Forgetting AI

The London Taxi Driver Study Connecting to AI: What Machines Still Can't Do Artificial neural networks face a problem biological networks solved: catastrophic forgetting. Train a network on task A, then train it on task B, and it forgets task A. But you can learn Spanish without forgetting English. How? The complementary learning systems theory proposes that hippocampus and cortex have different learning rates for good reason. Hippocampus learns fast but has limited capacity—it's the RAM. Cortex learns slowly but has vast capacity—it's the hard drive. The slow cortical learning prevents catastrophic forgetting by gradually interleaving new information with old. DeepMind's Deep Q-Network borrowed this biological insight, implementing experience replay similar to hippocampal sharp-wave ripples. The system stores experiences and replays them during training, allowing gradual integration without forgetting. Biology inspired the algorithm that defeated humans at Atari games.

> → Here are 4 main points from the text:
>
> → Artificial neural networks experience "catastrophic forgetting," where they lose old information when learning new tasks.
>
> → The complementary learning systems theory explains how human brains learn new information without forgetting old material.
>
> → This theory suggests the brain's hippocampus learns fast with limited memory, while the cortex learns slowly with vast storage capacity.
>
> → DeepMind's Deep Q-Network uses a biological method called "experience replay" to integrate new learning gradually and avoid forgetting.

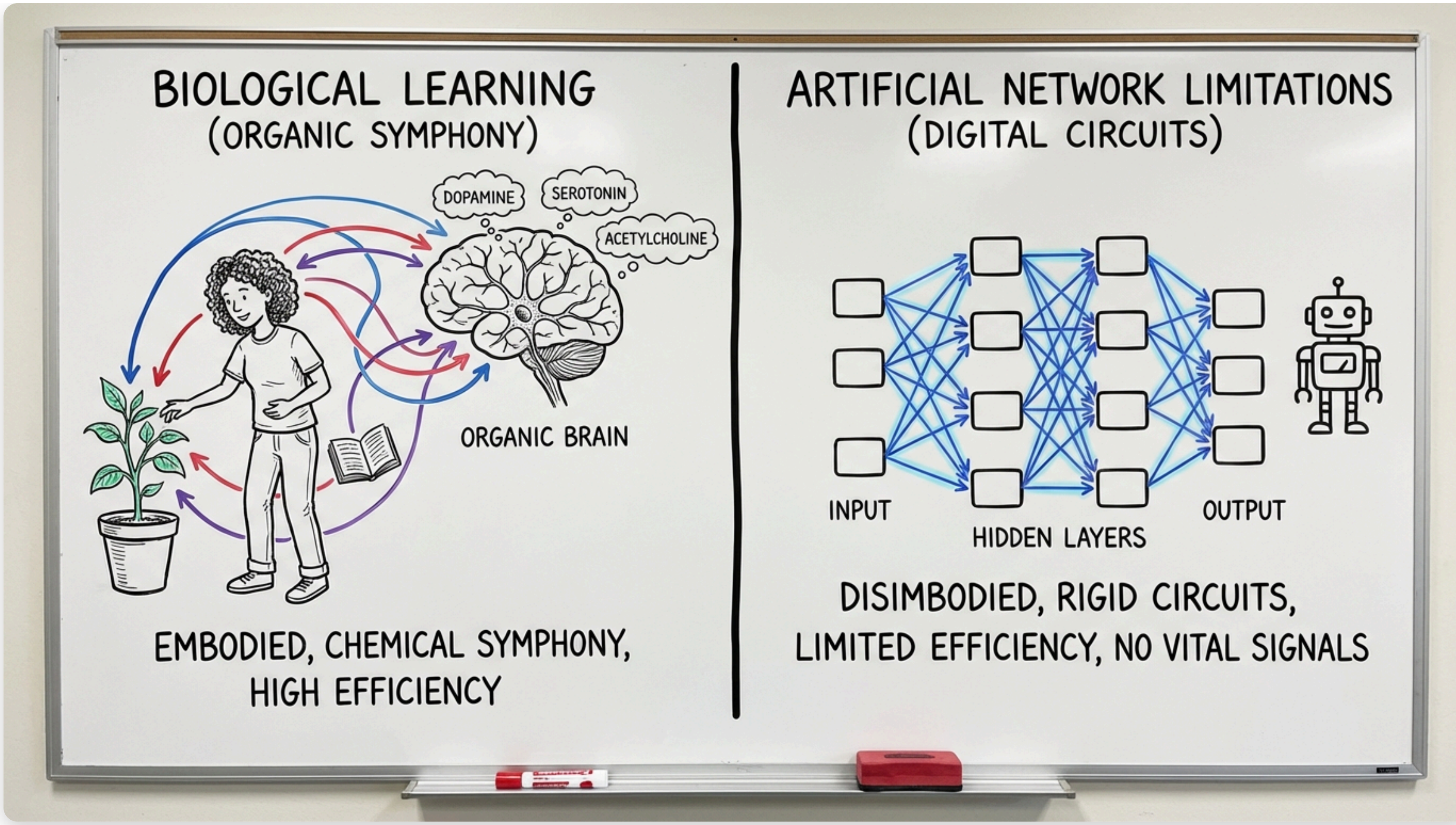


PANEL 1
CATASTROPHIC FORGETTING (AI)
AI BRAIN
TASK A
(e.g., Cat recognition)
TASK B
(e.g., Dog recognition)
Fading Knowledge
Overwritten / Lost
New Learning
PANEL 2
HUMAN MEMORY CONSOLIDATION
CORTEX
(Slow, Hard Drive-like)
New Experience
Long-Term Storage & Integration
HIPPOCAMPUS
(Fast, RAM-like)
Seamless Integration
PANEL 3
BIOLOGICAL INSPIRATION FOR AI
ADVANCED AI SYSTEM
(e.g., Deep Q-Network)
EXPERIENCE REPLAY BUFFER
HUMAN BRAIN MODEL
(Hippocampus & Cortex)
Mechanism: Re-learning past data
PANEL 4
DEEP Q-NETWORK (DQN) EXAMPLE
ATARI GAME
(e.g., Breakout)
Recalling Past Moves
Improvement & Mastery
DQN AGENT
Confident Mastery through Replay

AI Biological Limits

The London Taxi Driver Study But artificial networks still miss crucial elements. They lack energy constraints—backpropagation requires computing gradients that biology can't access. They lack neuromodulation—dopamine, serotonin, acetylcholine that gate plasticity. Most critically, they lack embodiment—the physical presence in the world that provides the temporal structure STDP depends on. We've captured some of biology's learning principles, but the full symphony remains uniquely biological.

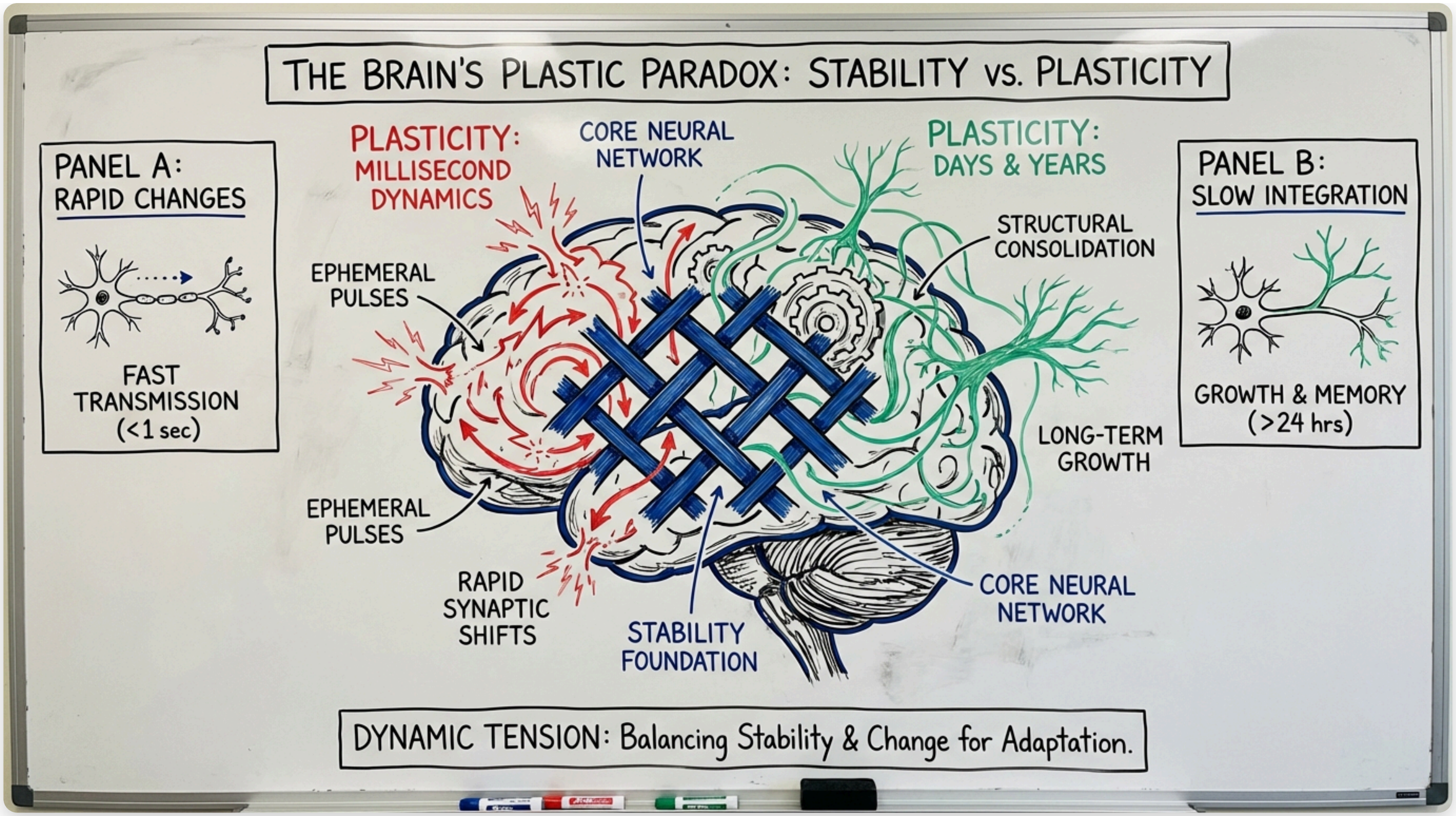
> - Here are 4 main points from the text:
> - Artificial neural networks use complex gradient calculations for learning. Biological brains learn differently, without needing these energy-intensive calculations.
> - Biological brains use specific chemicals like dopamine and serotonin to control how they learn and change. Artificial networks do not use these chemical signals.
> - Biological learning relies on a physical body interacting with the world over time. This physical presence creates the timing structures important for learning.
> - Artificial networks have copied some basic learning methods from biology. However, the complete and complex way biology learns is still unique.


BIOLOGICAL LEARNING
(ORGANIC SYMPHONY)
DOPAMINE
SEROTONIN
ACETYLCHOLINE
ORGANIC BRAIN
EMBODIED, CHEMICAL SYMPHONY, HIGH EFFICIENCY
ARTIFICIAL NETWORK LIMITATIONS
(DIGITAL CIRCUITS)
INPUT
HIDDEN LAYERS
OUTPUT
DISIMBODIED, RIGID CIRCUITS, LIMITED EFFICIENCY, NO VITAL SIGNALS

Plastic Paradox

The London Taxi Driver Study The Plastic Paradox: Engineering Challenge We face an engineering paradox that evolution spent 600 million years solving. How do you build a system that can learn without forgetting, adapt without losing identity, change while remaining stable? The solution isn't one mechanism but dozens, operating across different timescales. Millisecond spike timing, minute-long calcium dynamics, hour-long protein synthesis, day-long structural changes, year-long systems consolidation—each timescale handles different aspects of the stability-plasticity trade-off.

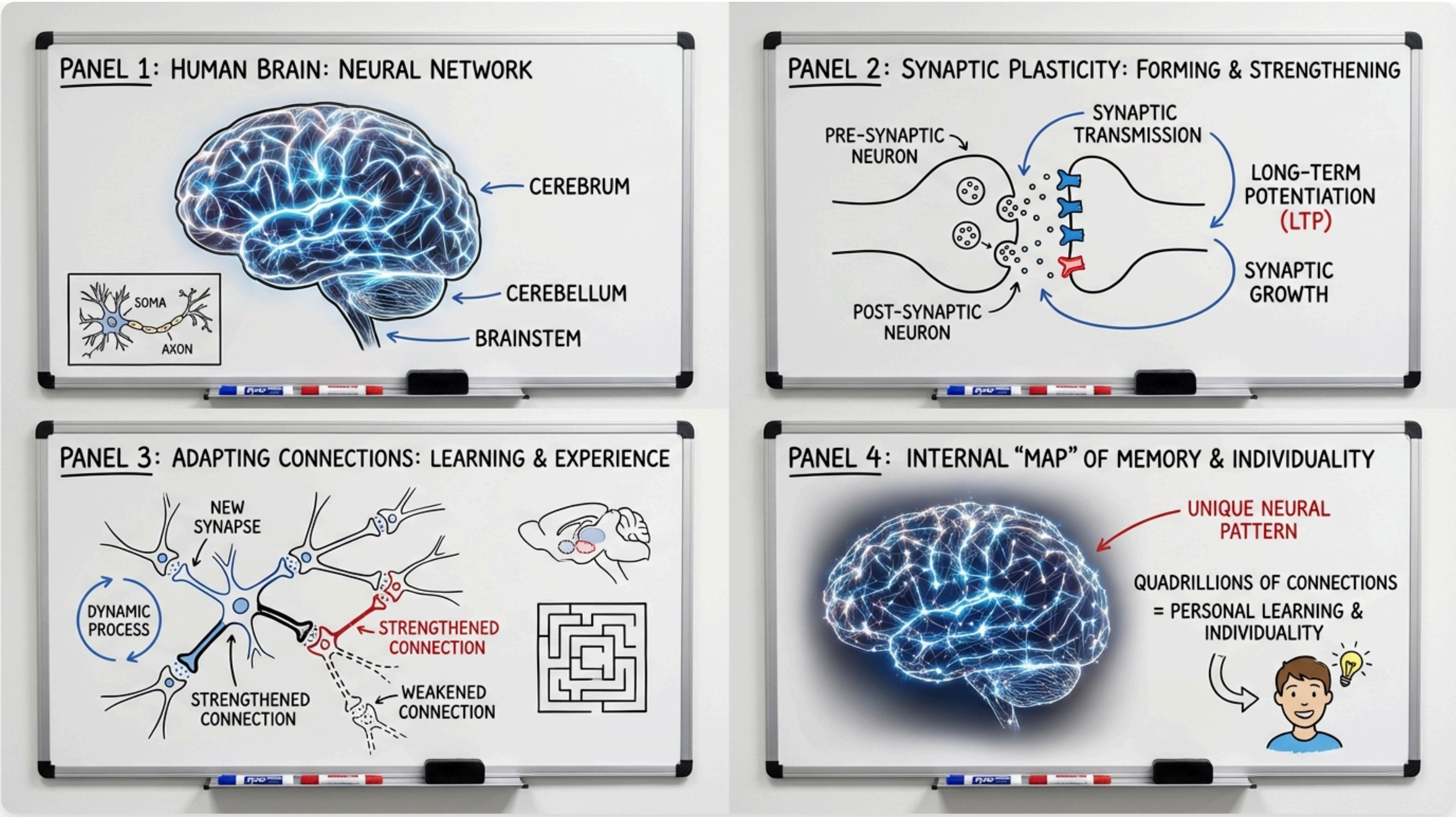
> - Here are 4 main points from the text:
> - Evolution developed a solution for a complex engineering challenge over 600 million years.
> - This challenge involves building a system that learns and adapts while staying stable and keeping its identity.
> - The brain solves this problem using many different mechanisms, not just one.
> - These mechanisms operate across various timescales, each balancing different aspects of change and stability.


THE BRAIN'S PLASTIC PARADOX: STABILITY vs. PLASTICITY
PANEL A: RAPID CHANGES
FAST TRANSMISSION (<1 sec)
PLASTICITY: MILLISECOND DYNAMICS
CORE NEURAL NETWORK
PLASTICITY: DAYS & YEARS
PANEL B: SLOW INTEGRATION
GROWTH & MEMORY (>24 hrs)
EPHEMERAL PULSES
STRUCTURAL CONSOLIDATION
EPHEMERAL PULSES
LONG-TERM GROWTH
RAPID SYNAPTIC SHIFTS
STABILITY FOUNDATION
CORE NEURAL NETWORK
DYNAMIC TENSION: Balancing Stability & Change for Adaptation.

Synaptic Plasticity Disorders

The London Taxi Driver Study Understanding synaptic plasticity isn't just academic curiosity—it's central to understanding neurological and psychiatric disease. Myasthenia gravis attacks the very machinery of synaptic transmission. Parkinson's disrupts the dopamine signals that gate plasticity. Schizophrenia may arise from an imbalance between excitation and inhibition, disrupting the delicate choreography of LTP and LTD. Depression, anxiety, PTSD—all involve disrupted plasticity. Most psychoactive drugs, from antidepressants to psychedelics, work by modulating synaptic plasticity. Consider the numbers: every postsynaptic neuron receives about 10,000 connections, each capable of independent plasticity. Multiply that by 86 billion neurons. That's roughly 1 quadrillion synapses, each a potential site of change. This combinatorial explosion of possibility is what makes every brain unique, every experience personal, every memory yours.

> - Here are 5 main points from the text:
> - Synaptic plasticity helps us understand brain and mental health diseases.
> - Many neurological and psychiatric diseases involve problems with synaptic plasticity.
> - Most psychoactive drugs change synaptic plasticity to achieve their effects.
> - The human brain contains roughly 1 quadrillion synapses, each able to change.
> - This huge ability for change makes every brain unique and creates our memories.

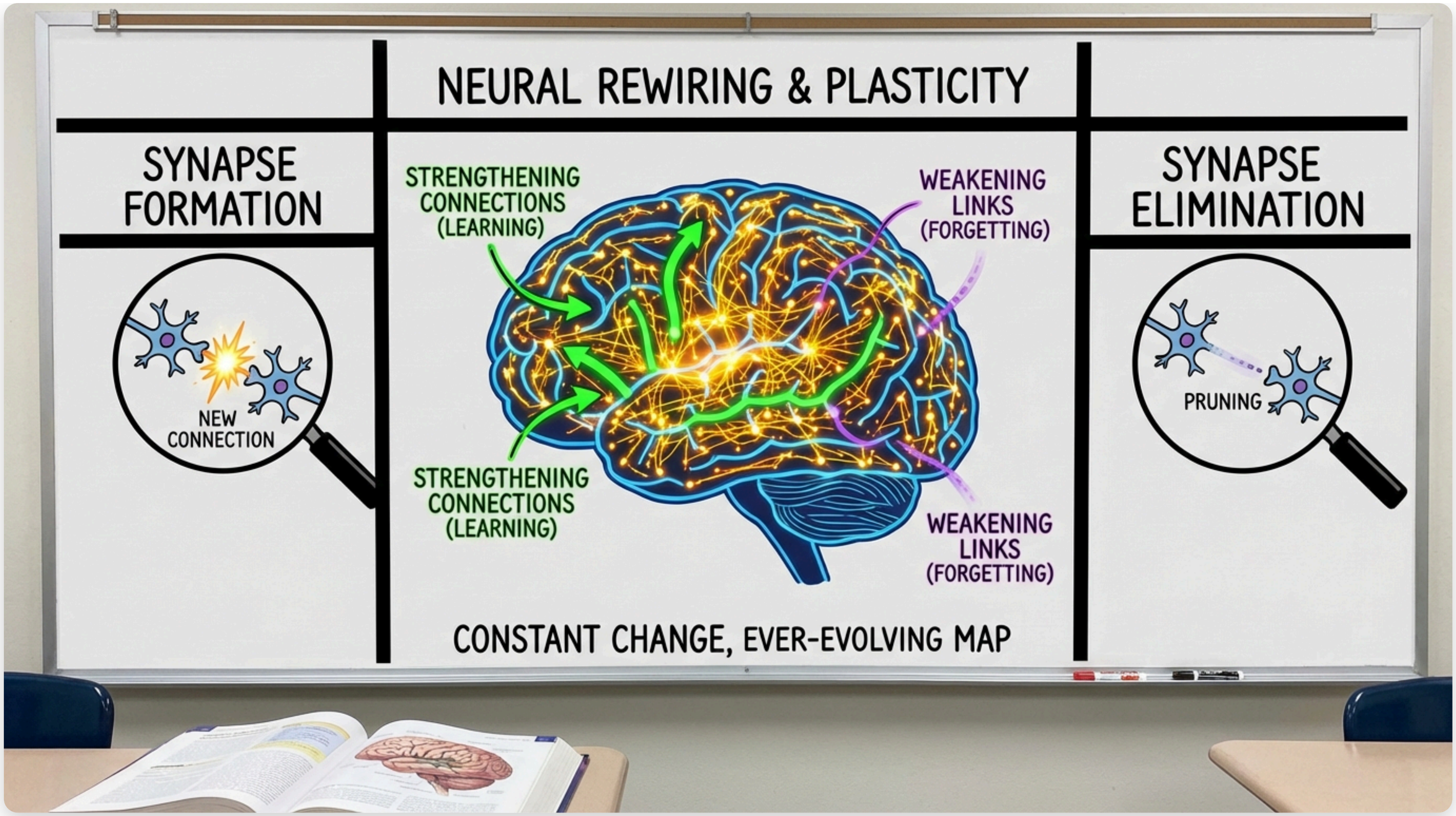


PANEL 1: HUMAN BRAIN: NEURAL NETWORK
CEREBRUM
CEREBELLUM
BRAINSTEM
SOMA
AXON
PANEL 2: SYNAPTIC PLASTICITY: FORMING & STRENGTHENING
PRE-SYNAPTIC NEURON
SYNAPTIC TRANSMISSION
LONG-TERM POTENTIATION (LTP)
SYNAPTIC GROWTH
POST-SYNAPTIC NEURON
PANEL 3: ADAPTING CONNECTIONS: LEARNING & EXPERIENCE
NEW SYNAPSE
DYNAMIC PROCESS
STRENGTHENED CONNECTION
STRENGTHENED CONNECTION
WEAKENED CONNECTION
PANEL 4: INTERNAL "MAP" OF MEMORY & INDIVIDUALITY
UNIQUE NEURAL PATTERN
QUADRILLIONS OF CONNECTIONS
= PERSONAL LEARNING & INDIVIDUALITY

Brain Plasticity

The London Taxi Driver Study Here's the beautiful terror of what we've learned today. Your brain contains approximately 100 trillion synapses. Every moment—right now, as I speak these words—these synapses are voting on who you'll become. Some are strengthening, encoding this moment. Others are weakening, letting go of what no longer serves. Some are disappearing entirely, making room for tomorrow's connections. You didn't just learn about plasticity today—you underwent it. The concepts we discussed literally rewired your brain. Neurons that had never fired together before are now connected. Synapses that were weak this morning are strong now. New proteins are being synthesized to lock in these changes. Tonight, while you sleep, these patterns will replay, transferring from hippocampus to cortex.

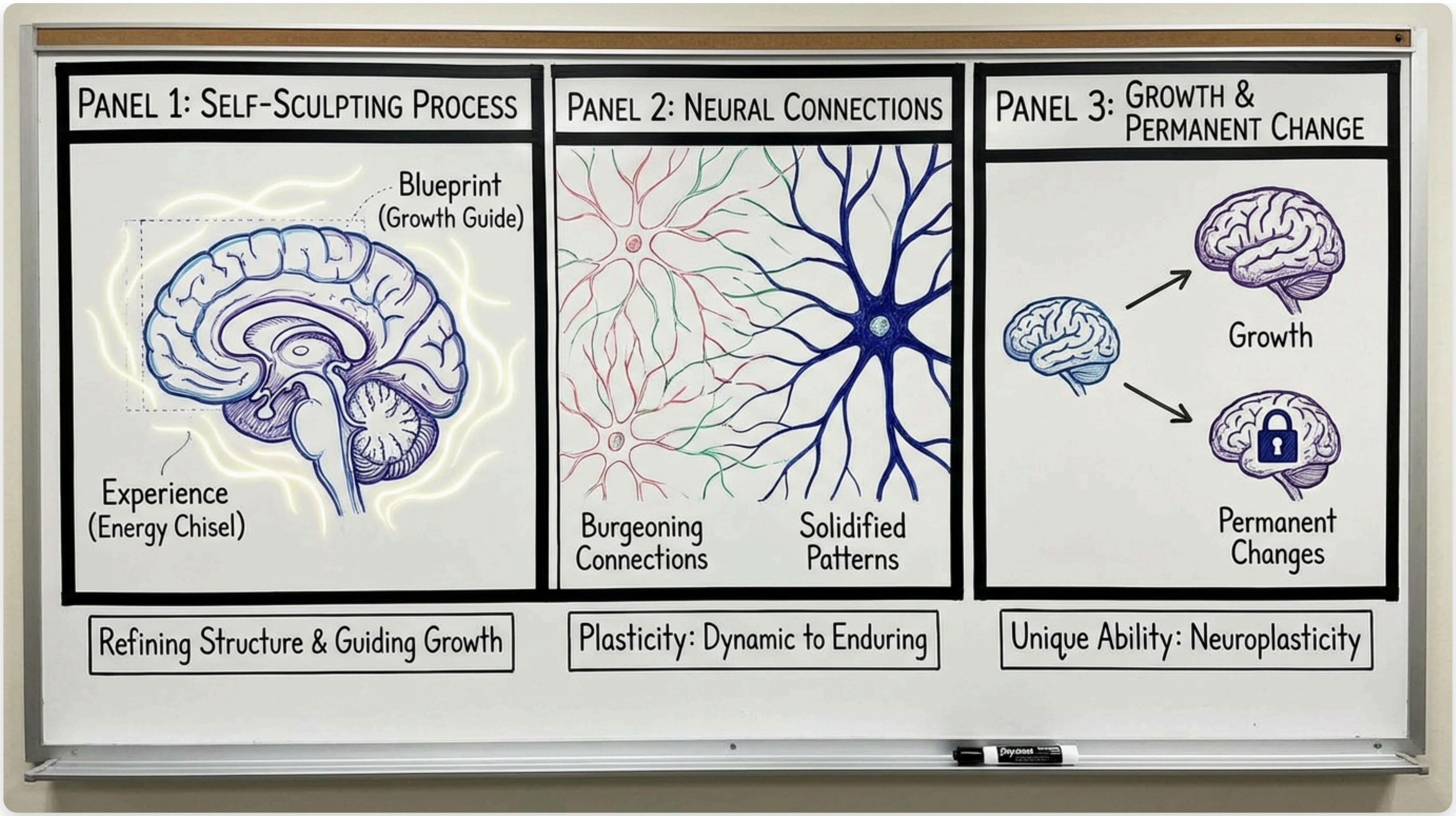
> - Here are 4 main points from the text:
> - Your brain contains about 100 trillion synapses.
> - Synapses in your brain constantly change by strengthening, weakening, or disappearing. These ongoing changes actively shape who you become.
> - Learning physically rewires your brain by creating new connections and strengthening existing ones.
> - Your brain synthesizes new proteins to make these changes permanent. During sleep, your brain consolidates new learning by replaying patterns.


NEURAL REWIRING & PLASTICITY
SYNAPSE FORMATION
NEW CONNECTION
STRENGTHENING CONNECTIONS (LEARNING)
WEAKENING LINKS (FORGETTING)
STRENGTHENING CONNECTIONS (LEARNING)
WEAKENING LINKS (FORGETTING)
SYNAPSE ELIMINATION
PRUNING
CONSTANT CHANGE, EVER-EVOLVING MAP

Brain Plasticity

The London Taxi Driver Study Cajal was right—we are the sculptors of our own brains. But unlike marble, which only loses material, the brain can also grow. Unlike clay, which remains soft, the brain can solidify changes. Unlike any material sculptors have ever worked with, the brain sculpts itself, using experience as both chisel and blueprint. The machinery of plasticity—from calcium influx to protein synthesis, from spine dynamics to systems consolidation—isn't just mechanism. It's the physical basis of learning, memory, identity, and change. It's what allows you to be different tomorrow than you are today, while still remaining you.

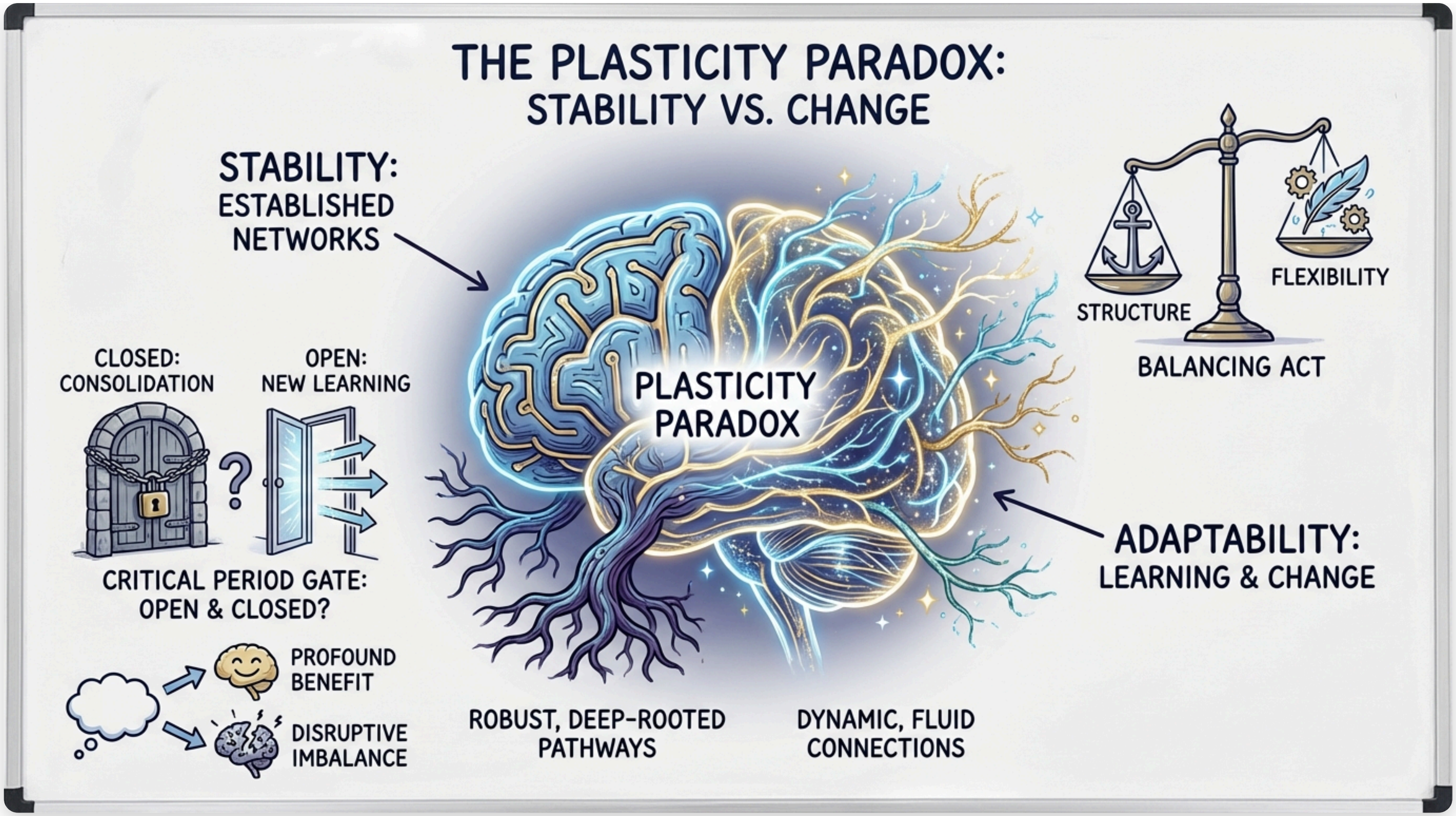
> - Here are the main points:
> - Our experiences actively shape and change our brains.
> - The brain can grow and make permanent changes based on new experiences.
> - Brain plasticity forms the physical basis for learning, memory, and personal identity.
> - This plasticity allows individuals to change and grow while still maintaining their core self.


PANEL 1: SELF-SCULPTING PROCESS
Blueprint
(Growth Guide)
Experience
(Energy Chisel)
PANEL 2: NEURAL CONNECTIONS
Burgeoning
Connections
Solidified
Patterns
PANEL 3: GROWTH &
PERMANENT CHANGE
Growth
Permanent
Changes
Refining Structure & Guiding Growth
Plasticity: Dynamic to Enduring
Unique Ability: Neuroplasticity

Brain Plasticity Paradox

The London Taxi Driver Study Thought Questions for Discussion Three questions to spark discussion before your next class: The Plasticity Paradox: Your brain must be stable enough to maintain your identity yet plastic enough to learn. How does the nervous system solve this fundamental tradeoff? Consider the roles of different timescales (milliseconds to years), different mechanisms (functional vs structural), and different brain regions (hippocampus vs cortex) in your answer. Why might disorders like autism or schizophrenia represent breakdowns in this balance? The Critical Period Dilemma: Critical periods allow rapid, dramatic reorganization during development but close to prevent disruption of established circuits. Should we develop drugs to artificially reopen critical periods in adults? What are the potential benefits (treating amblyopia, enhancing language learning) versus risks (destabilizing established abilities)? How might this change human society if widely available?

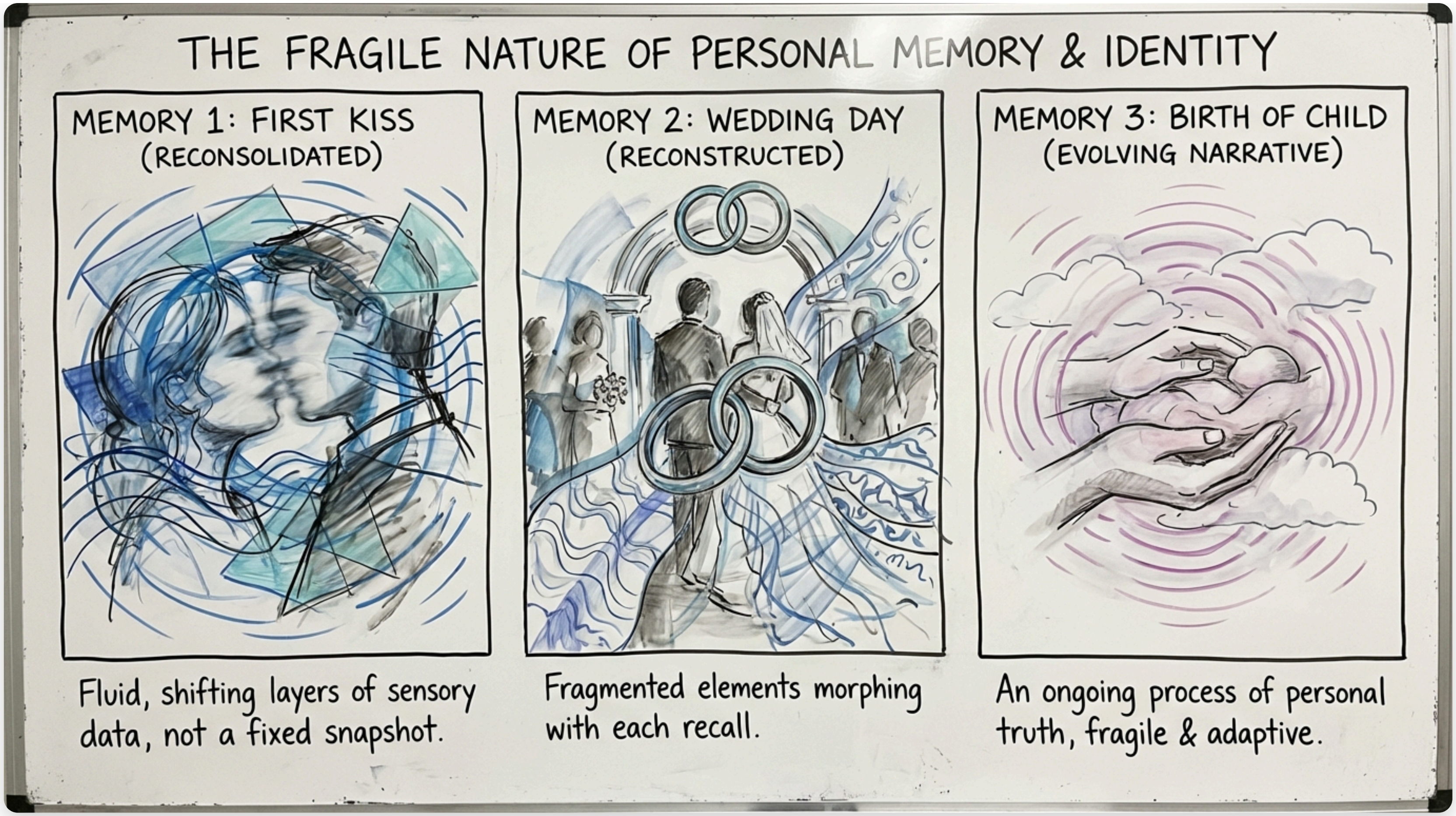
> → Here are 4 main points from the text:
> → The brain must balance being stable enough to maintain identity with being flexible enough to learn new things.
> → The nervous system manages this balance using various timescales, mechanisms, and different brain regions.
> → Critical periods are specific times during development when the brain undergoes rapid and dramatic reorganization.
> → These critical periods close to prevent disruption of the brain's established circuits.


THE PLASTICITY PARADOX:
STABILITY VS. CHANGE
STABILITY:
ESTABLISHED
NETWORKS
PLASTICITY
PARADOX
STRUCTURE
FLEXIBILITY
BALANCING ACT
CLOSED:
CONSOLIDATION
OPEN:
NEW LEARNING
CRITICAL PERIOD GATE:
OPEN & CLOSED?
ADAPTABILITY:
LEARNING & CHANGE
PROFOUND
BENEFIT
DISRUPTIVE
IMBALANCE
ROBUST, DEEP-ROOTED
PATHWAYS
DYNAMIC, FLUID
CONNECTIONS

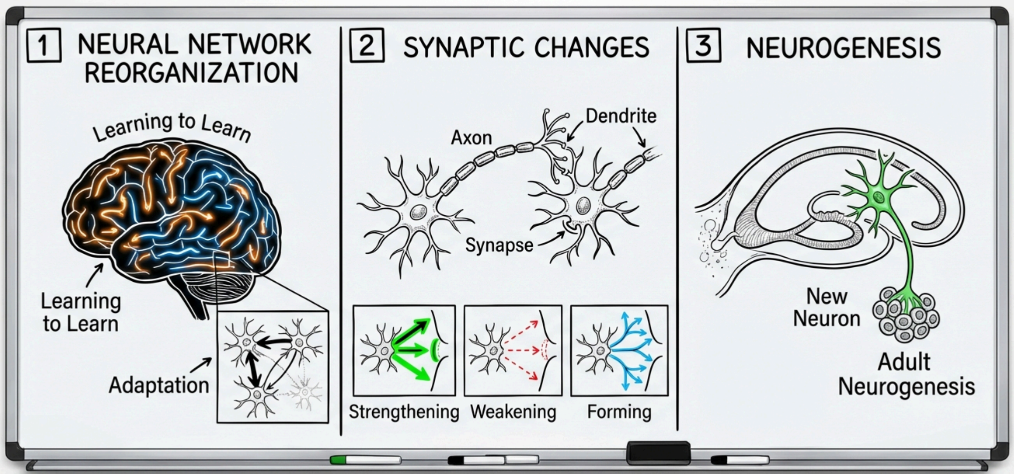
Memory Reconsolidation

The London Taxi Driver Study The Reconsolidation Problem: Every time you recall a memory, you potentially alter it. This means your most cherished memories—first kiss, wedding day, birth of children—may be composites of many recall events rather than faithful records of the original experience. Is this a bug or a feature of the memory system? How does this challenge our concepts of truth, identity, and legal testimony?

> - Here are 3 main points from the text:
> - Recalling a memory can change it.
> - Our most important memories become a mix of different recall events, not exact copies of the original experience.
> - Memory recall challenges our understanding of truth, identity, and legal testimony.


THE FRAGILE NATURE OF PERSONAL MEMORY & IDENTITY
MEMORY 1: FIRST KISS (RECONSOLIDATED)
MEMORY 2: WEDDING DAY (RECONSTRUCTED)
MEMORY 3: BIRTH OF CHILD (EVOLVING NARRATIVE)
Fluid, shifting layers of sensory data, not a fixed snapshot.
Fragmented elements morphing with each recall.
An ongoing process of personal truth, fragile & adaptive.

Neural Plasticity



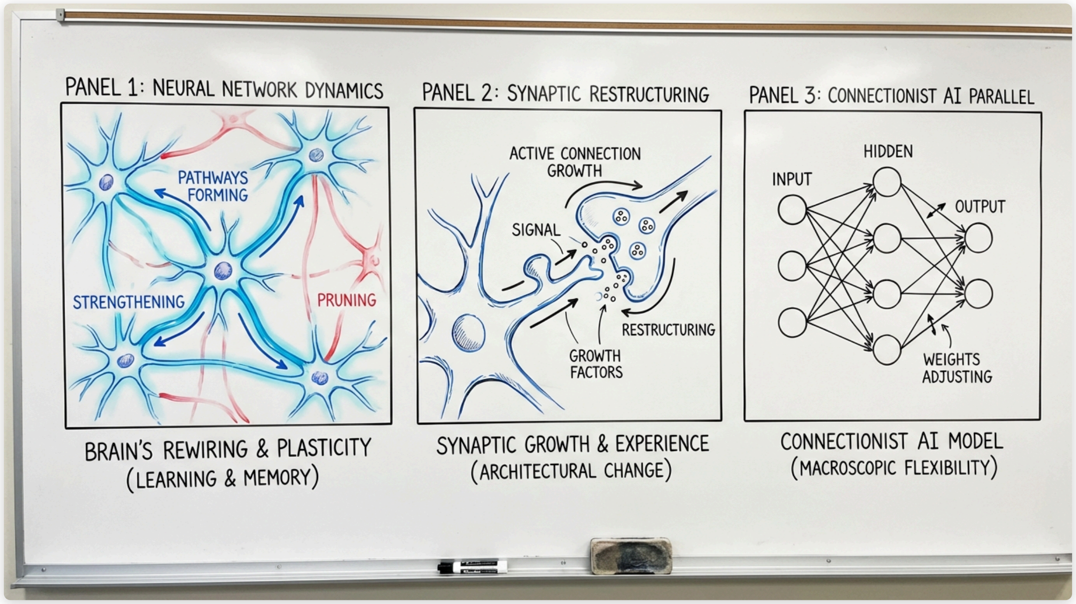
The brain's fluid, adaptive architecture throughout life.

- Here are 5 main points from the text:
- The brain's structure is dynamic and continuously ch throughout life.
- Learning and memory involve processes that strengt weaken connections between brain cells.
- Learning also involves precise molecular and structu changes within brain cells, such as altered connectic
- The brain has specific "critical periods" during devel when it is highly ready to learn certain skills.
- Even adult brains can generate new cells and reorgai existing parts based on new experiences.

Full Text

Neural Plasticity: How Brains Learn to Learn Neural Plasticity Visu Summary LECTURE OUTLINE (80 minutes) I. Cajal's Paradox & Fc Review (20 min) • Fixed architecture vs. dynamic function • Neura architecture, electrical & chemical signaling recap • Homosynapti heterosynaptic plasticity II. Long-Term Potentiation & Depression Bliss & Lømo's 1973 discovery • NMDA receptors as coincidence • LTD and the pianist who couldn't forget III. Molecular Machinery Memory (20 min) • Spike-timing dependent plasticity (STDP) • St plasticity: dendritic spines • Metaplasticity: learning how to learn Periods & Development (10 min) • Hubel & Wiesel's kittens • Gen tragedy and language acquisition • Indigenous songlines and perf V. Adult Neurogenesis & Repair (8 min) • 2000 new neurons daily taxi drivers and cortical remapping

Brain Plasticity

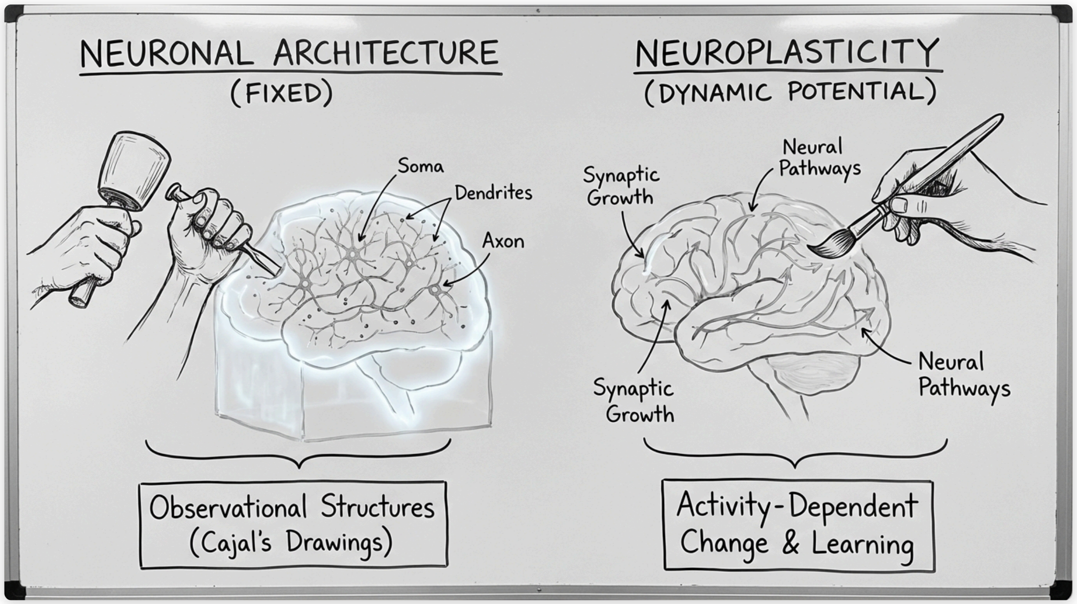


- Here are 3-5 main points from the text:
- Your brain constantly changes its physical structure your experiences.
- Learning and memory involve specific molecular proc that strengthen synaptic connections.
- Forgetting memories is an active and controlled proc like remembering.
- Daily habits, such as sleep and drinking coffee, affec your brain changes and learns.

Full Text

VI. Learning in Real Networks (7 min) • Memory consolidation and reconsolidation • AI/connectionism parallels and differences Your move at 120 meters per second, but your brain rewrites itself at tl of experience. Today we resolve Santiago Ramón y Cajal's paradc apparently fixed neural structures create infinite flexibility. You'll c that every word you hear is literally changing the physical structu synapses, that learning a new skill grows new brain tissue, and th forgetting is as precisely controlled as remembering. Through the choreography of long-term potentiation, we'll see how calcium in triggers protein synthesis that locks memories into synaptic archi We'll explore why critical periods exist—and how to reopen them- sleep is essential for spine pruning, and how your morning coffee the plasticity rules governing this very moment. From bacterial ac potentials to human consciousness, from Hebbian learning to arti intelligence, we'll trace the 3.8-billion-year evolution of learning i Prepare to understand why you can't tickle yourself, how meditati physically changes brain structure, and why every experience lea mark—but not equally.

Sculpting The Brain

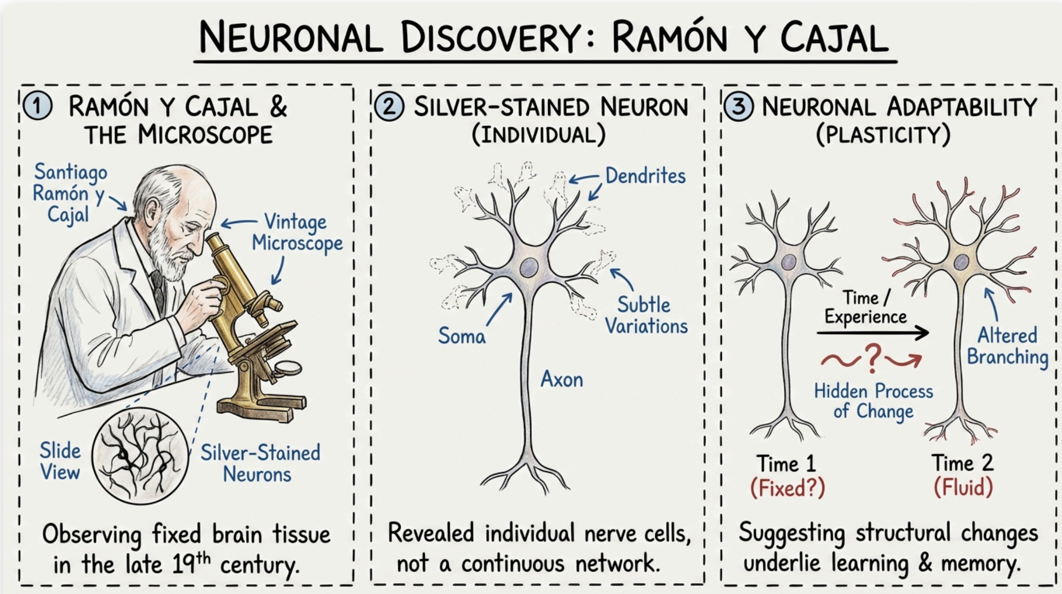


- Here are 3 main points from the text:
- The brain continuously shapes itself based on an ind
experiences.
- Early scientist Santiago Ramón y Cajal observed that
cells appeared fixed and unchangeable under his mi
- Despite his observations, Cajal believed individuals c
actively change and improve their own brains.

Full Text

Today's journey: From Cajal's 1894 drawings to 2024's real-time imaging. We'll discover how your brain sculpts itself using experie both chisel and blueprint. Opening: Cajal's Paradox Look at this d Santiago Ramón y Cajal spent thousands of hours at his microsco a technique he'd modified from Camillo Golgi, staining neurons w nitrate to reveal their architecture. Cajal saw what looked like fixe sculptures—beautiful, permanent, unchangeable structures froze biological glass. The neurons he drew in 1894 looked exactly like neurons he drew in 1904. Yet this same man wrote something tha have been impossible given what he was seeing: "Every man can, desires, become the sculptor of his own brain."

Brain Plasticity

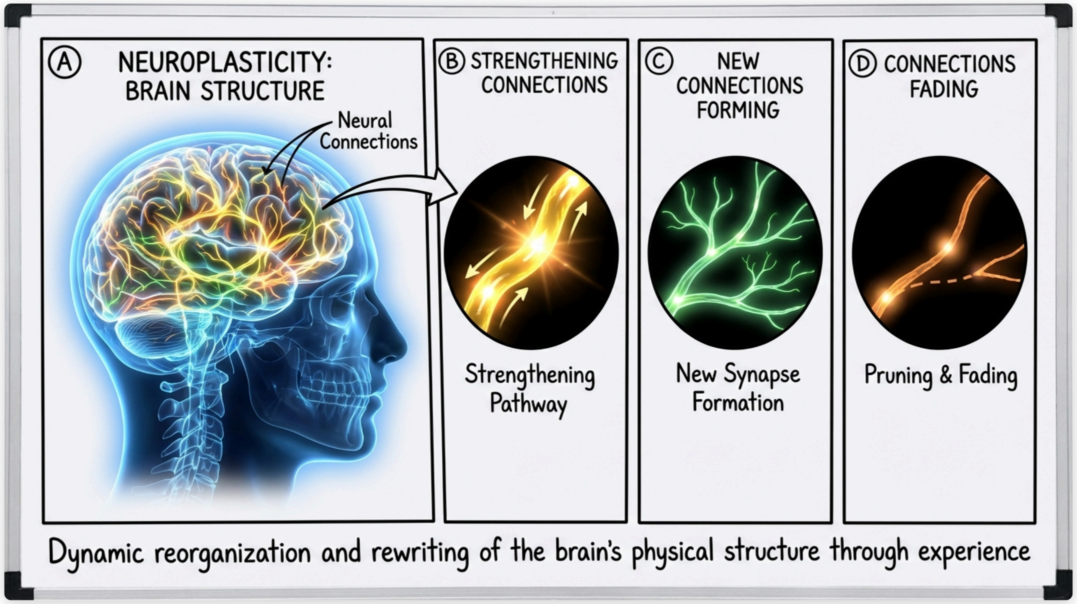


- Cajal noticed that the brains of musicians and schola
showed structural differences based on their activiti
- He also observed that neurons from young animals l
different from those in older animals.
- Cajal realized that while brain structure seemed stab
connections between neurons were fluid and change
- He was observing early signs of brain plasticity, ever
he lacked the tools to measure it directly.

Full Text

How could Cajal believe in brain sculpting when he was staring at
apparently fixed architecture? He had noticed something peculiar
preparations—neurons from musicians had denser dendritic trees
areas, neurons from scholars showed elaborations in association
and most mysteriously, neurons from young animals looked differ
old ones even when stained identically. The structure was stable,
something about the connections, their strength, their efficacy, w
Cajal was seeing the shadows of plasticity without having the too
measure it directly.

Brain Plasticity

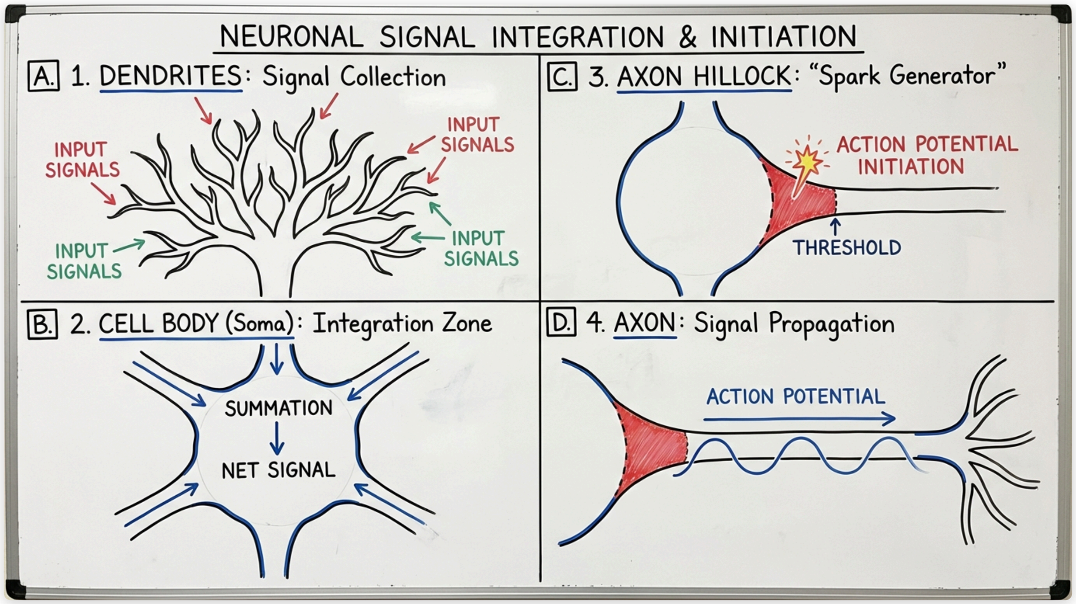


- Here are 4 main points from the text:
- Your brain constantly changes its physical structure.
- Neuroplasticity is the brain's ability to reorganize itse forming new connections throughout life.
- Every experience and new concept you learn literally your neural connections.
- Individual neurons generally stay in place, but their connections constantly strengthen, weaken, or disap

Full Text

Today, we're going to discover how your brain is rewriting itself at moment. Every word I speak, every concept you grasp, every mor confusion followed by clarity—all of these are literally changing th structure of your neural connections. Neural plasticity, or neuropl refers to the brain's ability to reorganize itself by forming new neu connections throughout life. You walked into this room with one b you'll leave with another. The question isn't whether your brain wi during this lecture—it's how much, where, and whether those cha last until tomorrow. The paradox that tortured Cajal has been resc the answer is more extraordinary than he imagined. Your neurons stay where they are—he was right about that—but their connectio strengthen, weaken, appear, and disappear in a choreography tha you who you are. The Symphony We've Built So Far Neural Archit Review

Neural Signal Integration

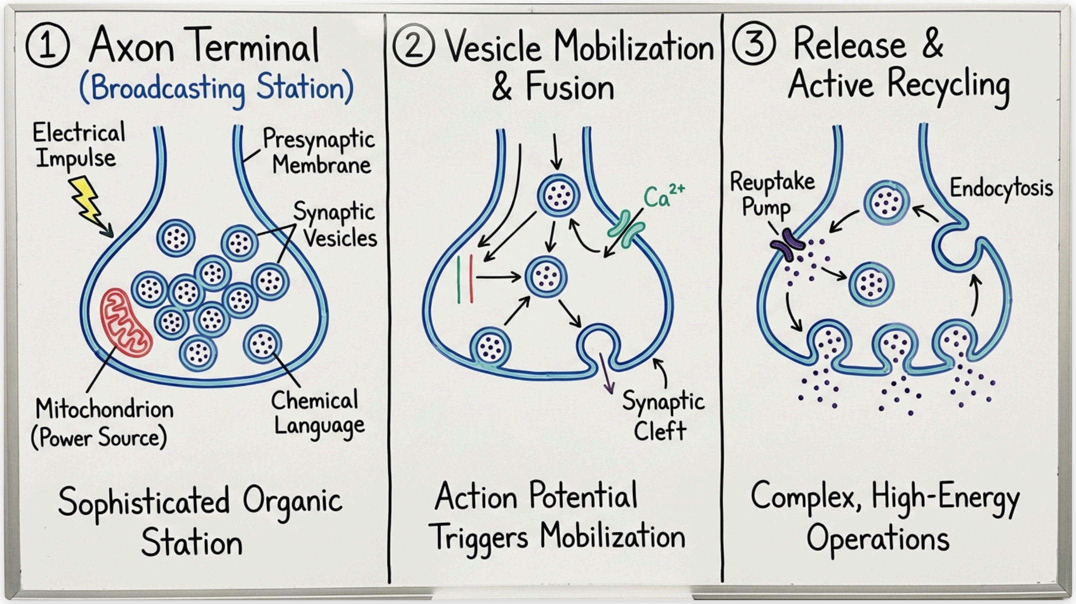


- Here are 4 main points from the text:
- Dendrites act as antennas, collecting signals from m neurons.
- These dendritic branches add up signals that arrive a locations or in quick succession.
- The cell body integrates all these signals to decide w the neuron fires.
- The axon hillock then generates the electrical impuls action potential, for the neuron.

Full Text

Let's reconstruct what we know about the hardware that makes p possible. The dendrites are the listeners of the neural world, spre roots to collect whispers from thousands of other neurons. Each branch acts as an antenna, but not a passive one—these structur spatial and temporal summation, adding signals that arrive at nea locations or in quick succession. The cell body, or soma, serves a integration zone where all these whispers get tallied into a single fire or don't fire. The axon hillock, that specialized region where t emerges, has the lowest threshold for action potential generation spark generator, the point of no return.

Axon Terminal Function

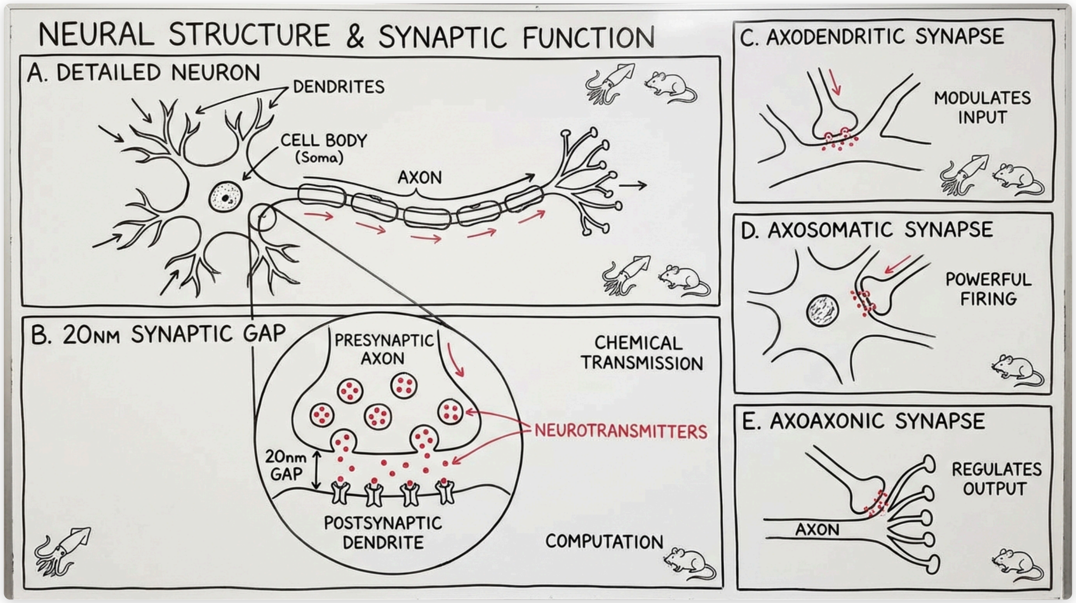


- Here are 4 main points from the text:
- The axon terminal converts electrical signals into che signals.
- It is a complex system with vesicles, specialized mac and recycling systems.
- Each part of the axon terminal is optimized for proce information and using energy efficiently.
- The brain uses 20% of the body's energy to maintair structures and their activity.

Full Text

The axon terminal is where the electrical signal gets translated in chemical language. This isn't just a wire touching another wire—it sophisticated broadcasting station with pools of vesicles ready tc specialized machinery for fusion, and recycling systems to sustai transmission. Each component is optimized for the fundamental t the nervous system: information processing versus energy consu Your brain uses 20% of your body's energy budget to maintain th structures and their activity.

Synapse Types

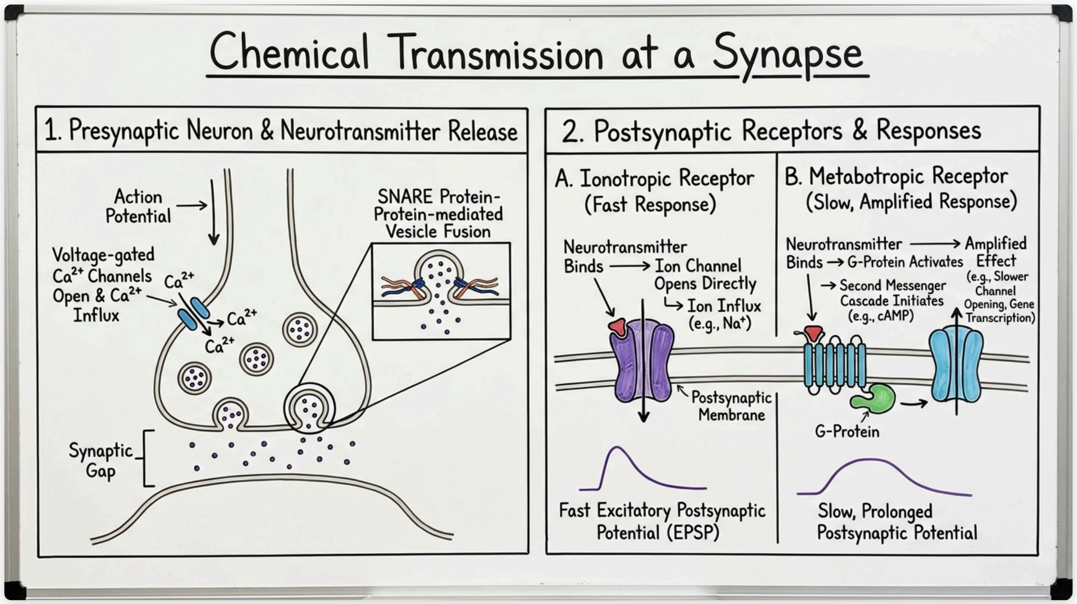


- Main Points:
- The synaptic gap performs the brain's main computa
- The nervous system contains three different types of synapses.
- Axodendritic synapses adjust input signals before th a neuron's body.
- Axosomatic synapses directly determine if a neuron
- Axoaxonic synapses regulate the function of other sy

Full Text

Chemical Transmission Mastery The synaptic gap is only 20 nano wide—that's 5,000 times thinner than a human hair—but it's wher computation happens. The nervous system has three types of syn each with different computational roles. Axodendritic synapses, t common, allow modulation of input signals before they reach the Axosomatic synapses, landing directly on the cell body, have pow immediate effects on whether a neuron fires. Axoaxonic synapses modulators, sitting on other synapses to regulate their function— mediate the heterosynaptic plasticity we'll explore today.

Chemical Transmission

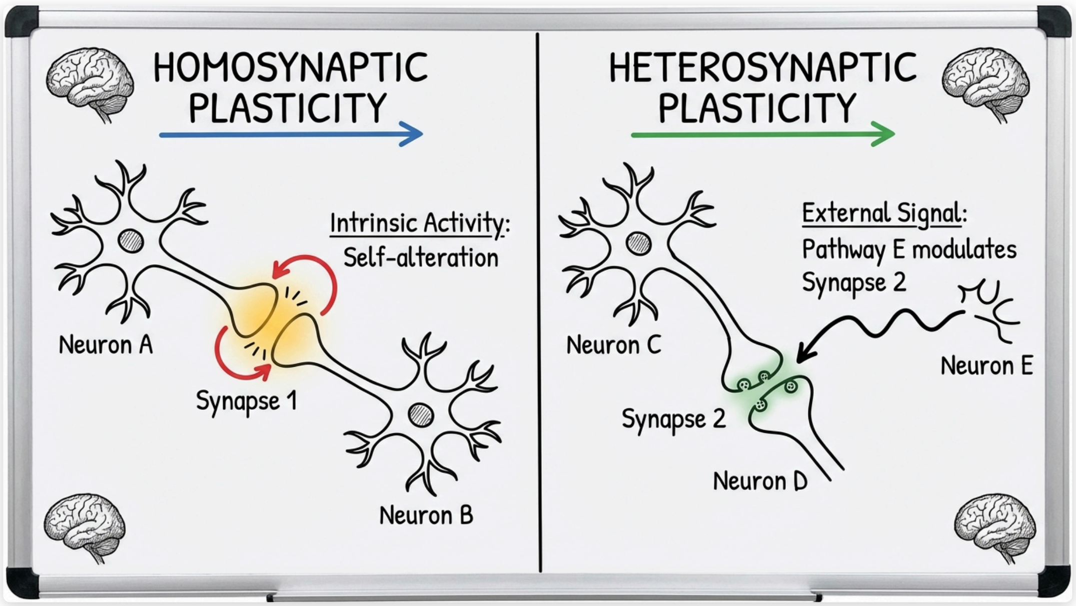


- Here are 3 main points from the text:
- When an action potential reaches the nerve terminal, enters and triggers the release of neurotransmitters.
- Ionotropic receptors directly open ion channels, crea responses in the cell.
- Metabotropic receptors trigger second messenger c producing effects that are slower but last longer and amplified.

Full Text

Chemical Transmission Mastery When an action potential reaches terminal, voltage-gated calcium channels open, and calcium rush calcium binds to sensor proteins that trigger SNARE proteins to z together, pulling vesicle membranes into the presynaptic membra dumping neurotransmitter into the gap. The elegance is in the rec types on the other side: ionotropic receptors like AMPA and NMD glutamate, or GABA-A for inhibition, directly open ion channels fo responses. Metabotropic receptors like mGluR or GABA-B trigger messenger cascades, trading speed for amplification and duratio Plasticity Revolution: How Experience Becomes Structure Two Fo Synaptic Plasticity

Synaptic Plasticity Forms

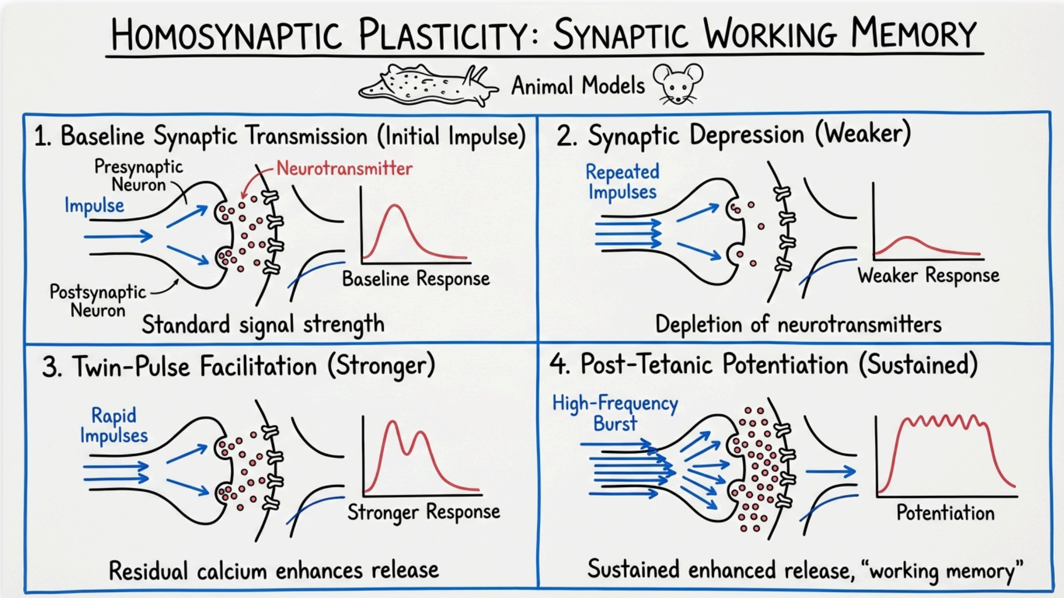


- Plasticity means something can be shaped or molde
- The nervous system shows two main types of plastic
- Homosynaptic plasticity occurs when a synapse cha based on its own activity.
- Heterosynaptic plasticity happens when other pathw activity changes a synapse.
- Synaptic plasticity changes the strength of connecti between neurons, for example through long-term po (LTP) and long-term depression (LTD).

Full Text

Chemical Transmission Mastery The word "plasticity" comes from "plastikos," meaning "capable of being shaped or molded." In the system, we see two fundamental forms of this moldability. Homos intrinsic plasticity refers to changes in synaptic strength brought the synapse's own activity—the synapse modifies itself based on history. Heterosynaptic or extrinsic plasticity involves changes tri activity in other pathways—the synapse is modified by external in These mechanisms of synaptic plasticity include changes in the s connections between neurons through processes like long-term potentiation (LTP) and long-term depression (LTD).

Homosynaptic Plasticity

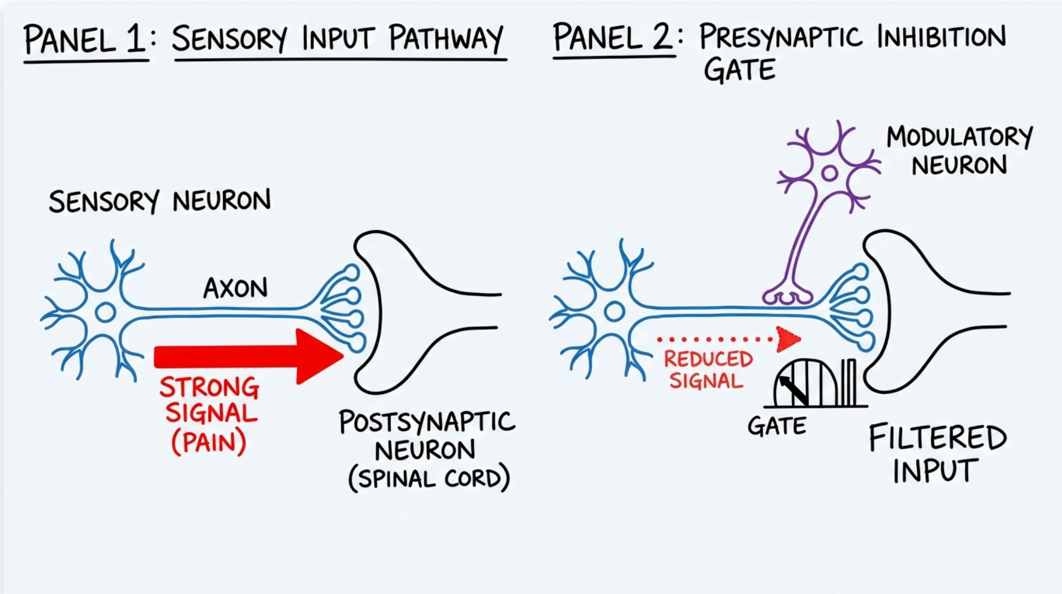


- Main Points:
- A neuron's signal weakens if it is stimulated again aft short delay. This weakening is called synaptic depres
- Closely spaced stimulations make a neuron's signal s This twin-pulse facilitation happens because calcium first pulse adds to the second.
- A rapid burst of stimuli can strengthen a synapse for minutes. This effect is known as post-tetanic potenti
- These short-term changes in synapses act as a work memory. They temporarily hold information.

Full Text

Chemical Transmission Mastery Let me demonstrate homosynapt plasticity with a simple experiment we've replicated thousands of Stimulate a sensory neuron once, and it produces a 1 millivolt EPS target motor neuron. Stimulate it again 200 milliseconds later, and second EPSP is only 0.7 millivolts—this is synaptic depression, ca depletion of readily-releasable vesicles. But if you wait just 20 mi between stimuli, the second EPSP is 2 millivolts—this is twin-puls facilitation, caused by residual calcium from the first pulse adding calcium from the second. Post-tetanic potentiation takes this furt Deliver a rapid train of stimuli—a tetanus—and the synapse remai strengthened for minutes afterward, even after the calcium has re baseline. The synapse remembers its recent intensive use. These term changes are the working memory of synapses, holding infor temporarily while longer-term mechanisms decide what's worth k

Presynaptic Control

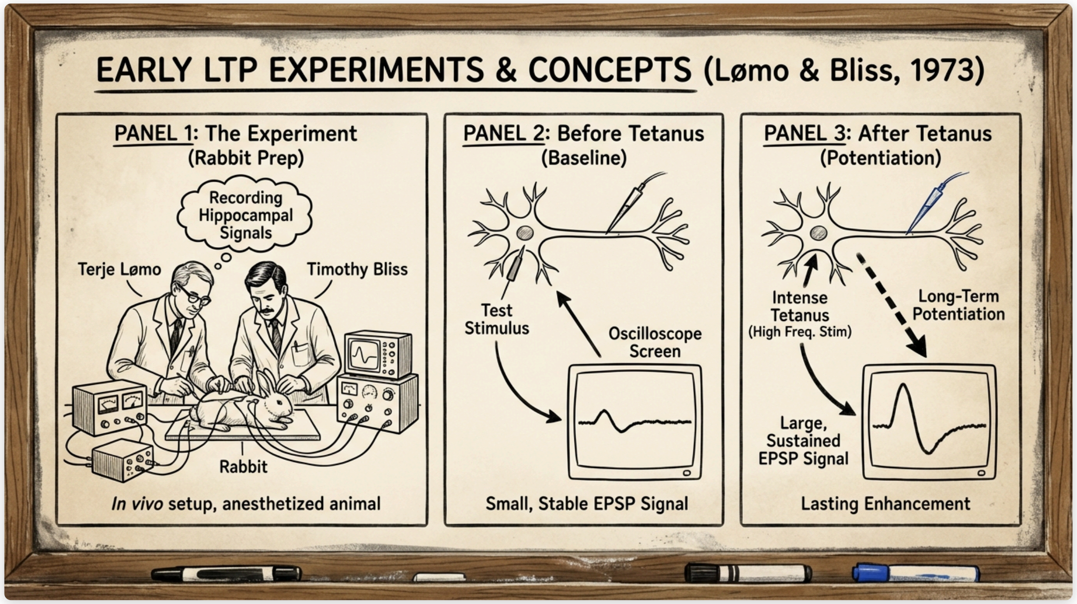


- Main Points:
- Heterosynaptic plasticity offers an additional method controlling chemical signals between neurons.
- Modulatory neurons use axoaxonic synapses to adju strength of nerve signals indirectly.
- The spinal cord uses presynaptic inhibition to filter s input, explaining why rubbing an injury reduces pain.
- Donald Hebb introduced the principle "Cells that fire wire together" in 1949.

Full Text

Chemical Transmission Mastery Heterosynaptic plasticity adds ar layer of control. A modulatory neuron making an axoaxonic synap transmission up or down without itself directly exciting or inhibitir postsynaptic cell. In the spinal cord, descending signals use pres inhibition to filter sensory input before it reaches the brain—this i rubbing an injury reduces pain. The gate is controlled before the enters. Donald Hebb crystallized the principle in 1949: "Cells that together, wire together." But he couldn't have imagined the molec machinery that would validate his prophecy. Long-Term Potentiati Discovery That Changed Everything

Long-Term Potentiation

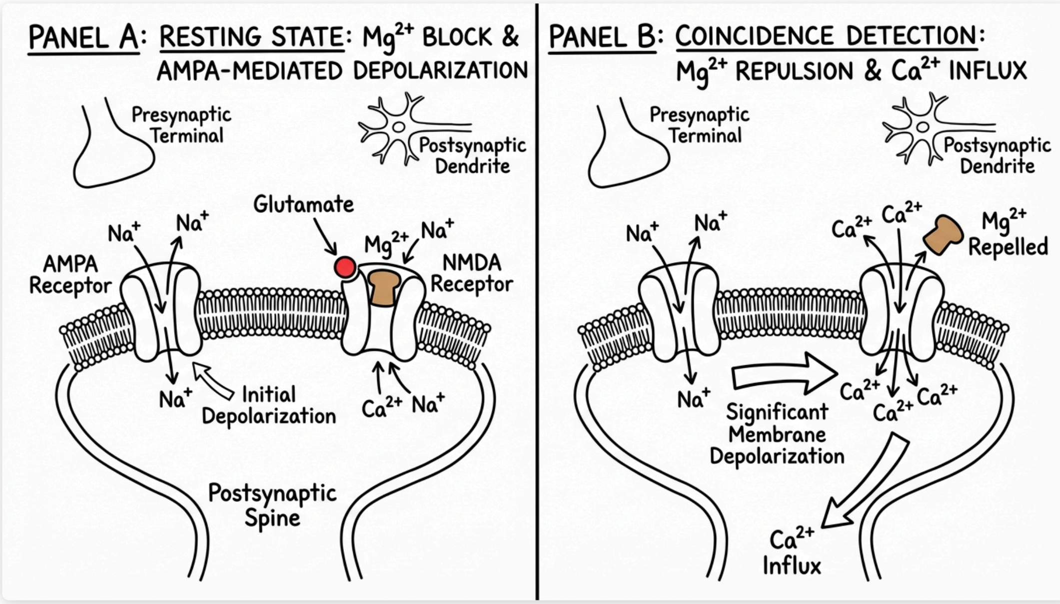


- Here are 4 main points from the text:
- In 1973, Lømo and Bliss discovered long-term potent (LTP).
- They studied memory by stimulating brain cells in anesthetized rabbits.
- A brief, intense stimulation made nerve cells respond more strongly to regular signals.
- This enhanced response lasted for a long time, helpi explain how memories are formed and stored.

Full Text

Chemical Transmission Mastery In 1973, two researchers in Oslo f changed how we think about memory. Terje Lømo and Timothy Bl working with anesthetized rabbits, recording from the dentate gy stimulating the perforant path from the entorhinal cortex. They w deliver a test stimulus every few seconds, recording a stable EPS 2 millivolts. Then they delivered their tetanus—100 pulses at 100 one second of intense stimulation. What happened next seemed i The same test stimulus that had produced 2 millivolt EPSPs befor tetanus now produced 5 millivolt responses. More remarkably, thi enhancement lasted for hours, sometimes days. They had discov term potentiation—LTP—the first physiological phenomenon with staying power necessary to explain memory.

NMDA Coincidence Detector

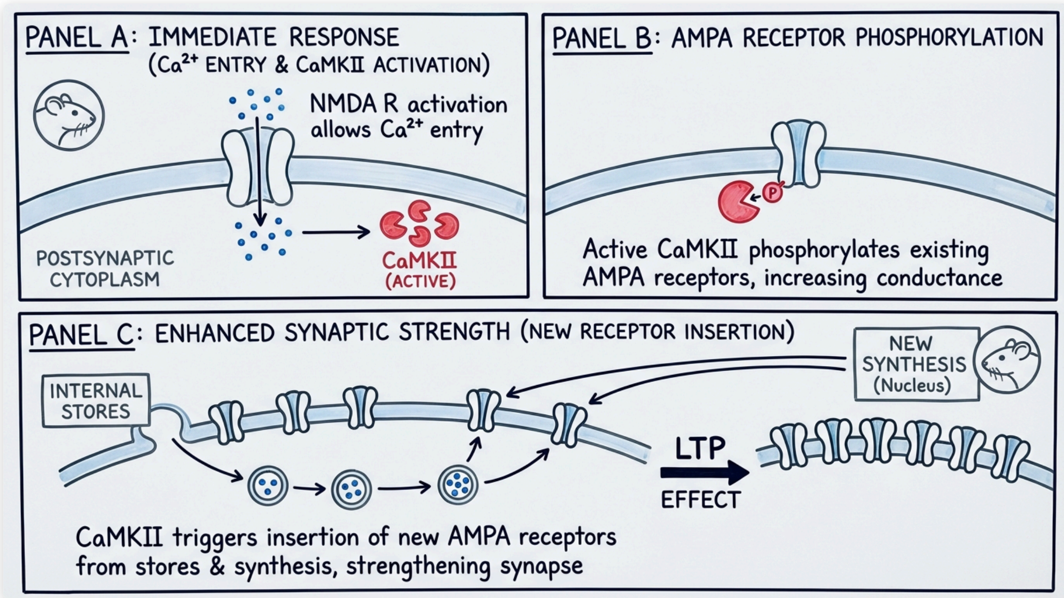


- Here are 4 main points from the text:
- Postsynaptic spines contain two types of glutamate r AMPA and NMDA.
- AMPA receptors open when glutamate binds, allowin to enter and depolarize the cell.
- NMDA receptors act as molecular coincidence detec to a unique blocking mechanism.
- At rest, magnesium blocks the NMDA channel; strong depolarization repels this block, allowing calcium to

Full Text

The NMDA Receptor: Nature's Coincidence Detector Let me show molecular choreography that makes LTP possible. The postsynap a typical CA3 to CA1 synapse in the hippocampus contains two ty glutamate receptors. AMPA receptors are straightforward—glutan the channel opens, sodium enters, causing depolarization. But NI receptors are molecular coincidence detectors with an elegant tri resting potential, a magnesium ion sits in the channel pore like a c bottle. Even if glutamate binds, no current flows—the magnesium everything. During weak stimulation, only AMPA receptors contrib response. But during a tetanus, something beautiful happens. Th and spatial summation of many inputs depolarizes the postsynap membrane significantly. As the inside of the cell becomes less ne reaching about -35 millivolts, the magnesium ion is electrically re from its binding site. The NMDA channel opens, and calcium flood

AMPA Potentiation

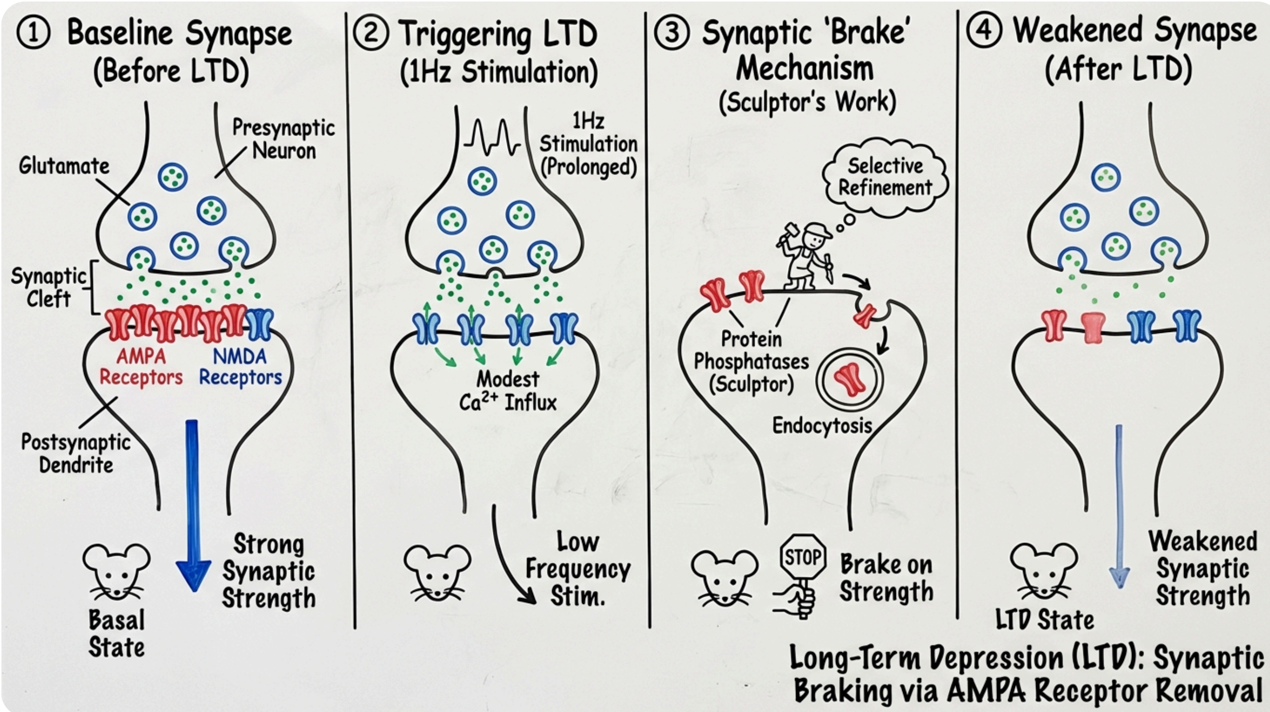


- Here are 3 main points from the text:
- Calcium triggers changes that make existing recepto sensitive and add new ones. This results in a stronge response to a signal.
- Early-phase LTP involves changes to existing protein lasts hours. Late-phase LTP creates new proteins, la days or weeks.
- Your hippocampus decides which information becom term memory. It does this by triggering the creation proteins.

Full Text

The NMDA Receptor: Nature's Coincidence Detector This calcium trigger for everything that follows. It activates calcium/calmodulin dependent kinase II (CaMKII), which phosphorylates existing AMF receptors, making them more sensitive. More dramatically, it trigg insertion of entirely new AMPA receptors into the membrane. Son pulled from internal stores, others are synthesized on demand. Tl that the same presynaptic release of glutamate now activates mo receptors, producing a larger response. The distinction between phase LTP, lasting 1-3 hours and requiring only post-translational modifications, and late-phase LTP, requiring new protein synthesi lasting days to weeks, mirrors the distinction between short-term term memory. Your hippocampus is deciding right now which part lecture deserve protein synthesis.

Long-Term Depression

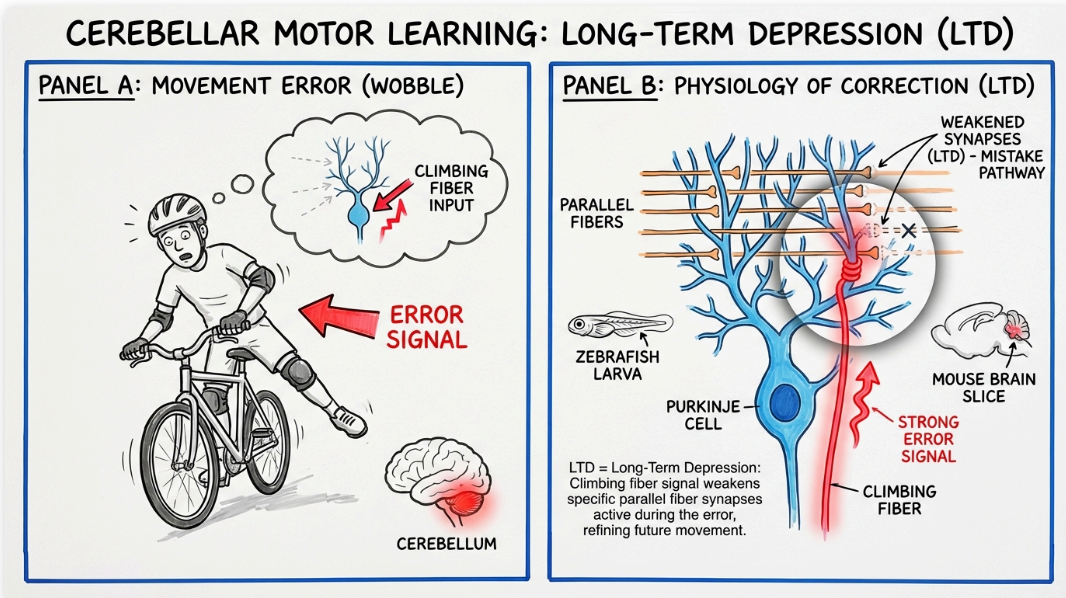


- Here are 4 main points from the text:
- Long-term depression (LTD) acts like a brake for syn strength, balancing the strengthening effects of LTP.
- LTD prevents synapses from becoming oversaturate allowing them to encode and store new information.
- Prolonged low-frequency stimulation, such as 1 Hz fo minutes, triggers LTD.
- This stimulation causes a modest calcium influx, acti phosphatases that reduce AMPA receptor sensitivity remove them from the cell membrane.

Full Text

The NMDA Receptor: Nature's Coincidence Detector Long-Term Depression: The Art of Forgetting If LTP is the accelerator of syna strength, long-term depression (LTD) is the brake—and you need drive effectively. A synapse that could only strengthen would satu losing its ability to encode new information. LTD isn't forgetting; i selective refinement, the neural equivalent of a sculptor removing marble. The induction protocol is LTP's mirror image: instead of b frequency stimulation, LTD requires prolonged low-frequency stir typically 1 Hz for 15 minutes. This produces a modest calcium infl enough to activate phosphatases but not kinases. The phosphata remove phosphate groups from AMPA receptors, making them les sensitive, and trigger the removal of receptors from the membran

Cerebellar Motor Learning

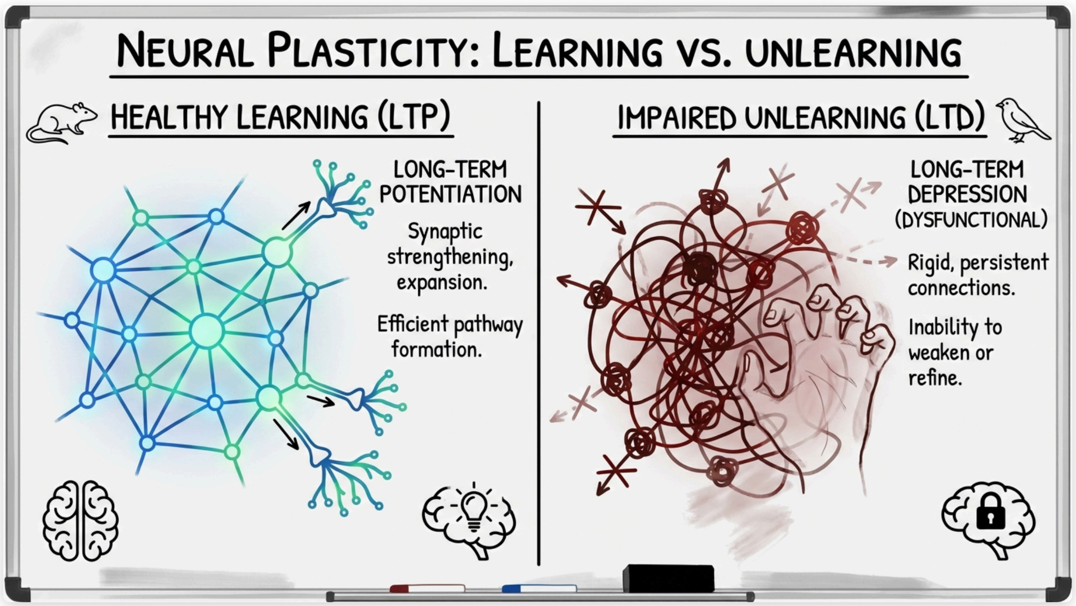


- Here are 3-5 main points from the text:
- The cerebellum uses a process called LTD (long-terr depression) to help with motor learning.
- When you make a movement error, climbing fibers se teaching signal to brain cells.
- These teaching signals cause LTD, weakening the sy linked to the error.
- Weakening specific synapses helps the brain learn fr mistakes and improve motor skills, like riding a bike.

Full Text

The NMDA Receptor: Nature's Coincidence Detector The cerebell turned LTD into an art form for motor learning. Every time you ma movement error, climbing fibers from the inferior olive deliver a te signal to Purkinje cells, inducing LTD at the parallel fiber synapse caused the error. This is how you learned to ride a bicycle—by we the synapses that produced wobbles and falls.

NMDA Receptor Failure

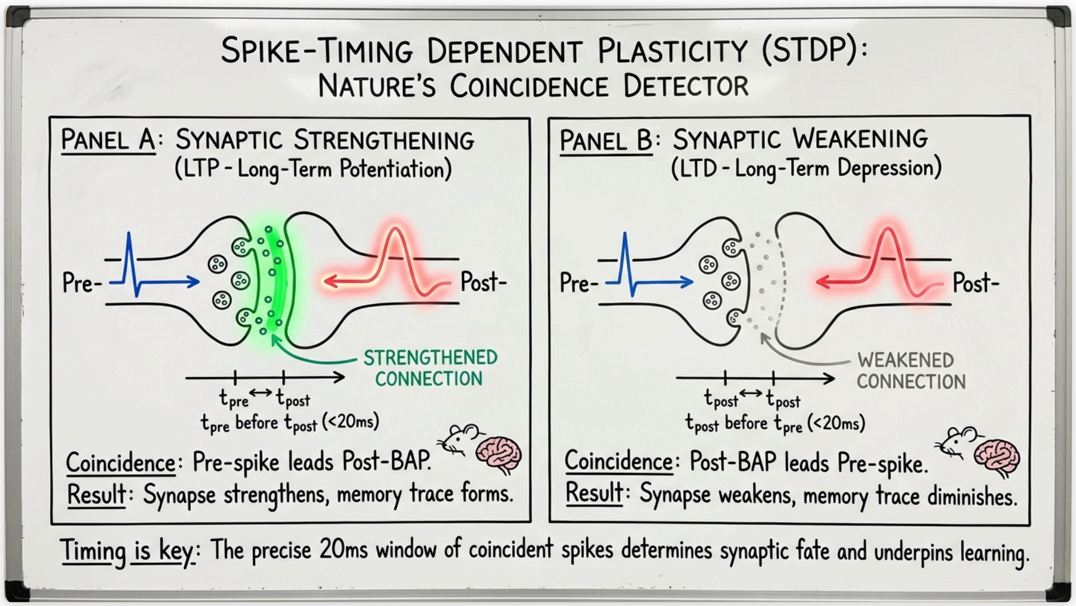


- Here are 4 main points from the text:
- Long-Term Depression (LTD) allows the brain to wea connections it no longer needs.
- The brain's ability to weaken inappropriate connectio vital as its ability to strengthen useful ones.
- Dysfunction in Long-Term Depression (LTD) is a com factor in autism spectrum disorders and schizophren
- The brain functions as both a learning and an unlear machine.

Full Text

The NMDA Receptor: Nature's Coincidence Detector Let me tell y Sarah, a composite of several patients I've studied. Sarah was a c pianist who developed focal dystonia—her fourth and fifth fingers involuntarily curl when she tried to play scales. The tragedy wasn movement disorder; it was that her brain couldn't unlearn the abn pattern. The LTD mechanisms that should have weakened the err connections were impaired. She could still strengthen synapses t LTP, learning new pieces, but she couldn't erase the pathological programs. Her career ended not because she couldn't learn, but l she couldn't forget. This dysfunction in LTD is emerging as a com theme in autism spectrum disorders and schizophrenia. The abilit weaken inappropriate connections is just as important as strengtl appropriate ones. The brain is not just a learning machine—it's a l and unlearning machine. The Molecular Machinery of Memory Spi Dependent Plasticity (STDP)

Synaptic Timing

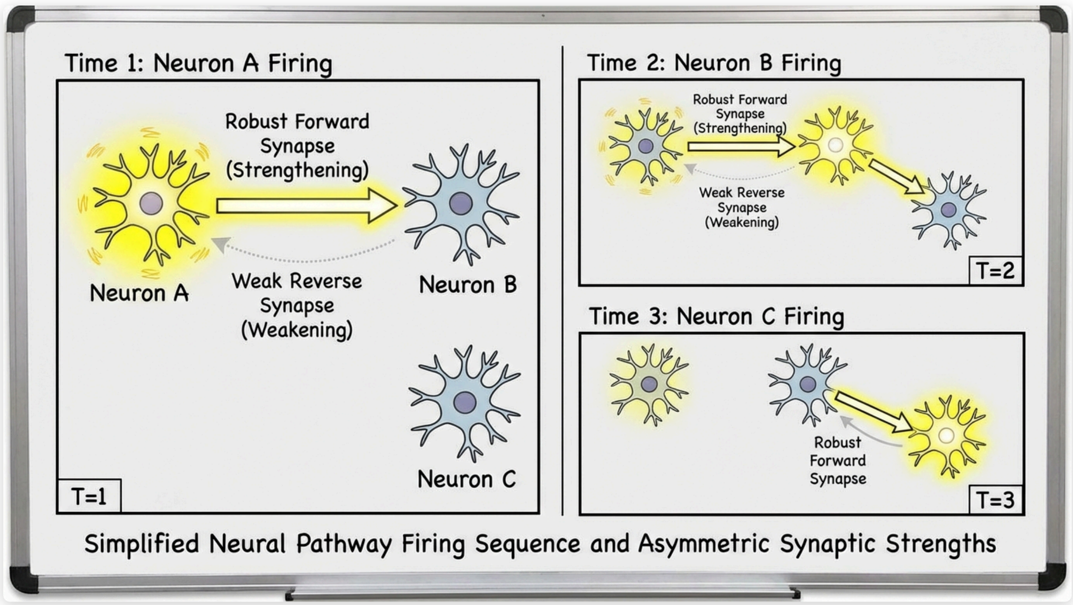


- Here are 4 main points from the text:
- Synapses in the brain strengthen or weaken dependi exact timing of electrical signals.
- A synapse strengthens when an incoming signal arriv before the neuron fires, and it weakens when the sig arrives just after.
- This rapid process, called spike-timing dependent pl uses millisecond differences to influence whether me form or fade.
- When a neuron fires, it sends signals backward to its dendrites, telling all its synapses that it has just fired

Full Text

The NMDA Receptor: Nature's Coincidence Detector The brain fa credit assignment problem: when a neuron fires, which of the tho inputs that preceded it should be strengthened? The answer is breathtakingly precise. If a presynaptic spike arrives just before a postsynaptic spike—within 20 milliseconds—that synapse is stren The input is credited with contributing to the output. But if the pr spike arrives just after the postsynaptic spike, the synapse is wea The input couldn't have caused the output, so its influence is redu spike-timing dependent plasticity operates on the scale of millise difference of 10 milliseconds can determine whether a synapse st or weakens, whether a memory forms or fades. The mechanism ir backpropagating action potentials—when a neuron fires, the signa just go forward down the axon, it also propagates backward into t dendrites, announcing to all synapses: "The cell just fired."

NMDA Sequence Learning

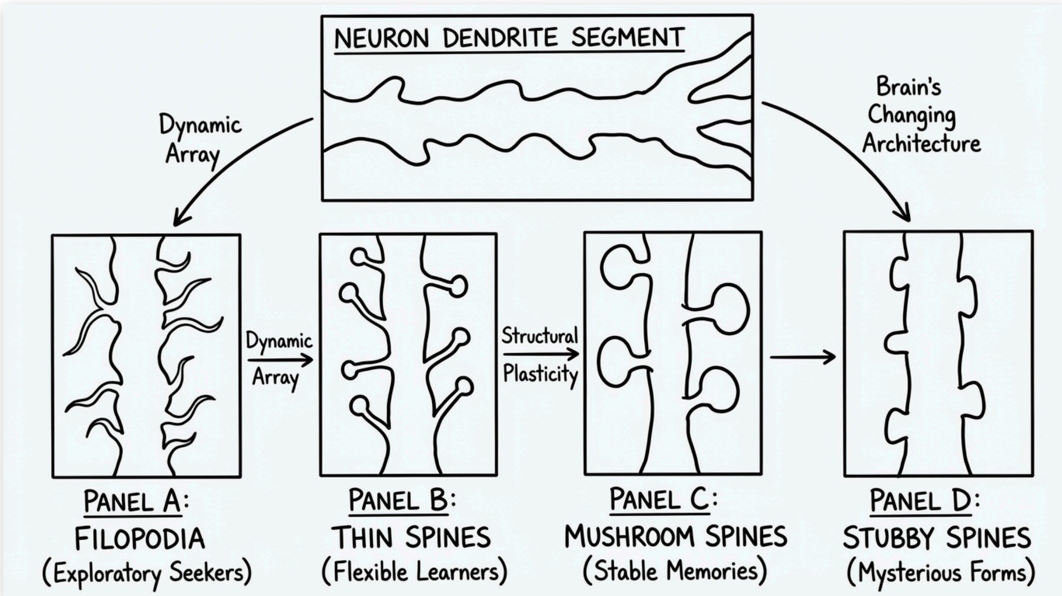


- Here are 3 main points from the text:
- The NMDA receptor helps the brain learn sequences detecting when neurons fire together in a specific or
- Neurons strengthen their connections when they cor fire one after another in a specific sequence.
- The brain encodes learned sequences as an asymme pattern of strong synaptic connections.

Full Text

The NMDA Receptor: Nature's Coincidence Detector This timing explains how you learn sequences. When you memorized your ph number, neurons representing each digit fired in sequence. The s from the "5" neuron to the "5" neuron was strengthened because consistently fired just before "5." The reverse connections were w The sequence became encoded in the asymmetric pattern of syn strengths.

Structural Plasticity

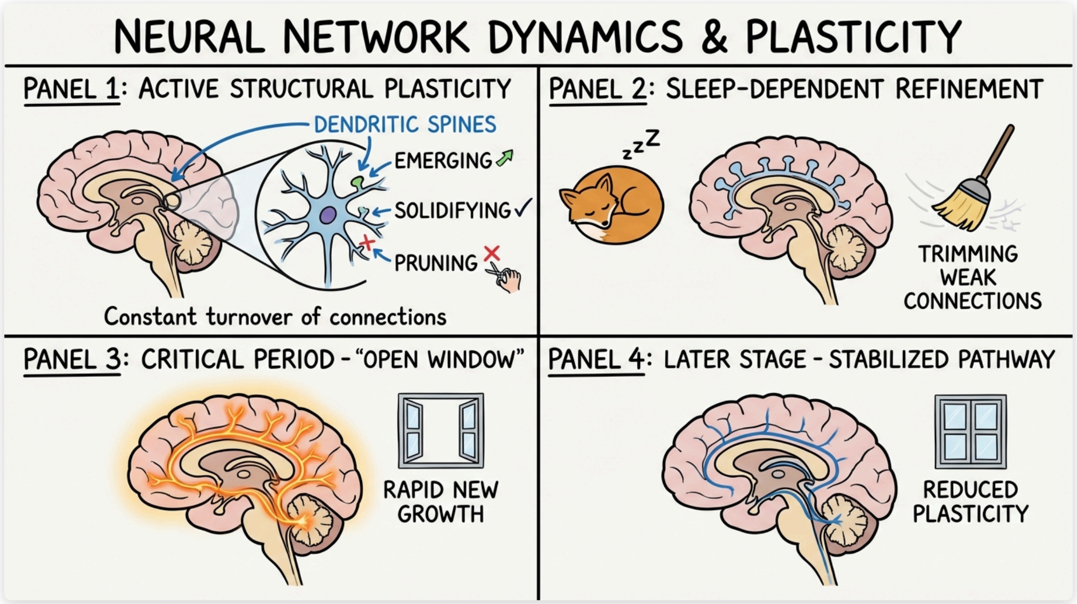


- Main Points:
- Structural plasticity means the brain's physical archi changes.
- Dendritic spines are dynamic structures in the brain connections form.
- Filopodia are seeker spines that actively look for new connections.
- Thin spines help the brain learn quickly, and mushro store long-term memories.

Full Text

Structural Plasticity: The Shapeshifters We've been talking about changes—the same structures working differently. But the brain a undergoes structural plasticity—the physical architecture itself ch Dendritic spines, those tiny protrusions where excitatory synapse the most dynamic structures in your brain. Spines come in distinc each with different functions. Filopodia are the seekers—thin, hig projections that sample the environment for new synaptic partner extending and retracting over minutes. Thin spines are the learne structures with small heads that can rapidly strengthen or weake activity. Mushroom spines are the memories—large, stable structu big heads that can persist for months or years. Stubby spines re mysterious, neither clearly learning nor remembering, possibly se reserve pool.

Structural Plasticity

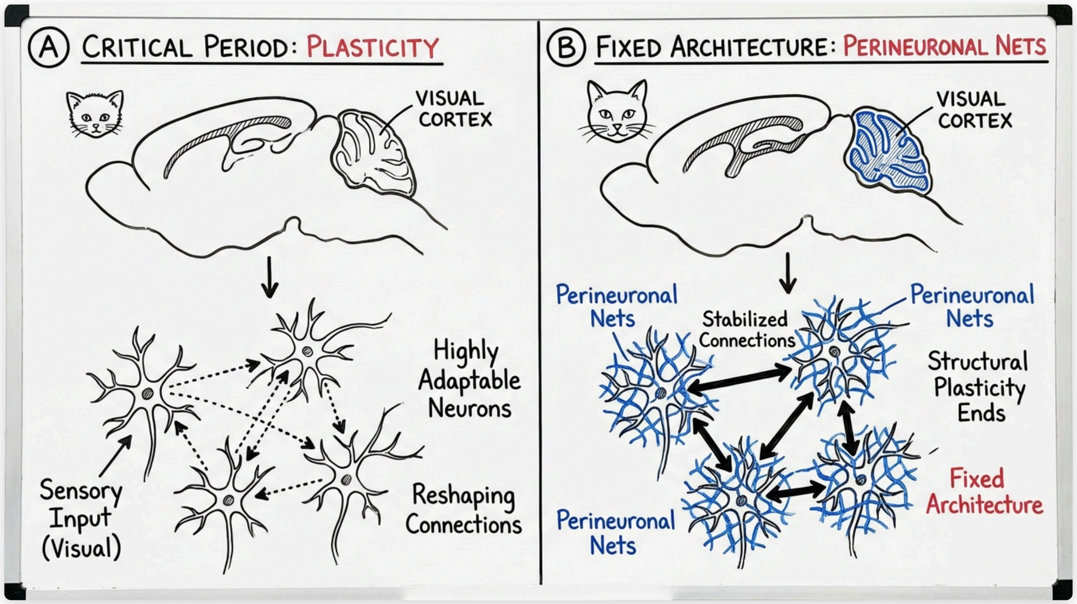


- Here are 3 main points from the text:
- Brain connections called spines continuously appear disappear in living brains, especially when learning n
- During sleep, the brain strengthens important conne and eliminates weak ones. This process helps to imp memory.
- Experiments show that early life experiences signific permanently shape brain development, such as how pathways form.

Full Text

Structural Plasticity: The Shapeshifters Two-photon microscopy h revealed a truth that would have stunned Cajal: spines appear anc disappear in living brains over hours. In motor cortex during skill l 10-15% of spines turn over daily. During sleep, weak spines are se eliminated while strong ones are preserved—your brain literally pr connections while you dream. This is why sleep deprivation impai memory; without pruning, the signal-to-noise ratio deteriorates. C Periods: Windows of Opportunity Hubel and Wiesel's Kittens Davi and Torsten Wiesel's experiments in the 1960s were elegant in de troubling in implication. They sutured one eye closed in newborn then examined the visual cortex weeks later. What they found rev neuroscience: neurons that should have responded to both eyes r responded only to the eye that had remained open. The deprived gone blind—the retina was fine—but the cortical territory had bee conquered by the experienced eye.

Visual Critical Plasticity

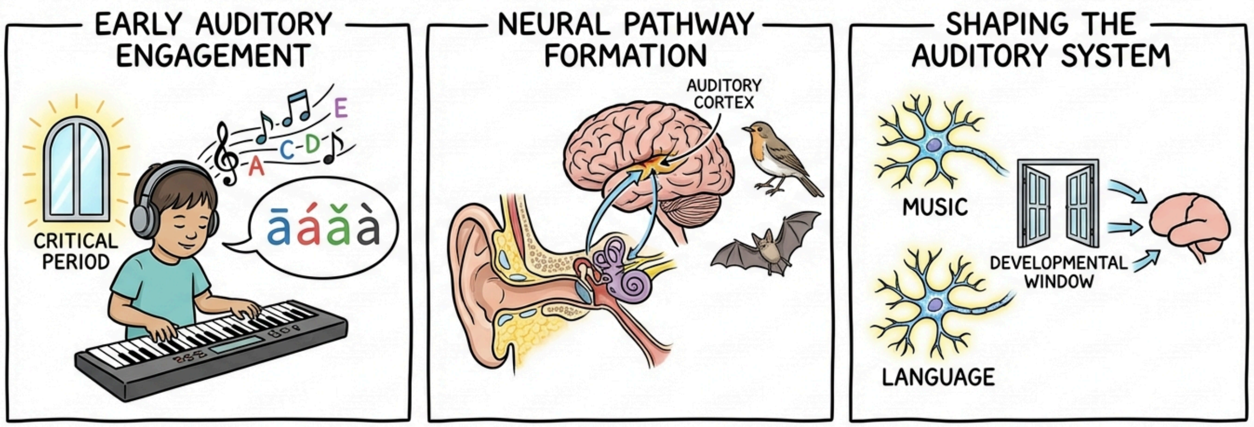


- Main Points:
- Visual experience during a critical period physically s
  the brain's visual architecture.
- This critical period lasts until about age seven in hum
- Untreated eye problems in children during this time c
  permanent "lazy eye" because the brain reassigns its
  territory.
- Specialized perineuronal nets end the critical period
  neurons.

Full Text

Structural Plasticity: The Shapeshifters The crucial discovery was
The same deprivation in adult cats had minimal effect. There was
period, from about 3 weeks to 3 months in cats, when visual expe
literally shaped the physical architecture of visual cortex. Miss thi
and the organization became permanent. In humans, this critical p
extends to about age seven. Children with cataracts or strabismu
eyes) must be treated early or face permanent amblyopia—"lazy e
because the eye is lazy, but because the brain has reassigned its
The molecular brake that ends this period involves perineuronal n
specialized extracellular matrix structures that literally cage neuro
restricting structural plasticity.

Ability Critical Periods

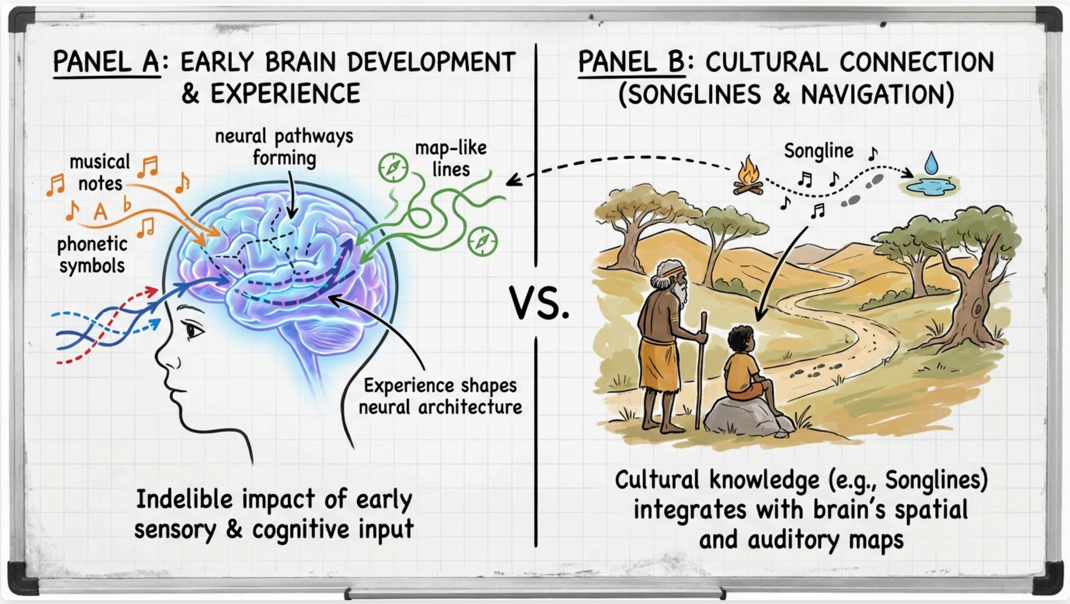


- Here are 3 main points from the text:
- Humans have a critical period for learning language. this period permanently diminishes one's ability to d normal language skills.
- Children who begin musical training before age seve more likely to develop perfect pitch.
- Speakers of tonal languages like Mandarin are much likely to have perfect pitch. Their early language exp tunes their auditory system differently.

Full Text

Language and Perfect Pitch The story of Genie haunts neuroscier Discovered in 1970 at age 13, she had been locked in isolation sin months old, never spoken to, never taught language. Despite inte therapy, she never developed normal language abilities. Her trage demonstrated that human language has a critical period—miss it, capacity is permanently diminished. Perfect pitch provides a more window into critical periods. Children who begin musical training l seven are far more likely to develop absolute pitch—the ability to produce notes without a reference. But here's the fascinating par speakers of tonal languages like Mandarin, where pitch carries m nine times more likely to have perfect pitch. Their language exper during the critical period tunes their auditory system differently.

Auditory Brain Shaping

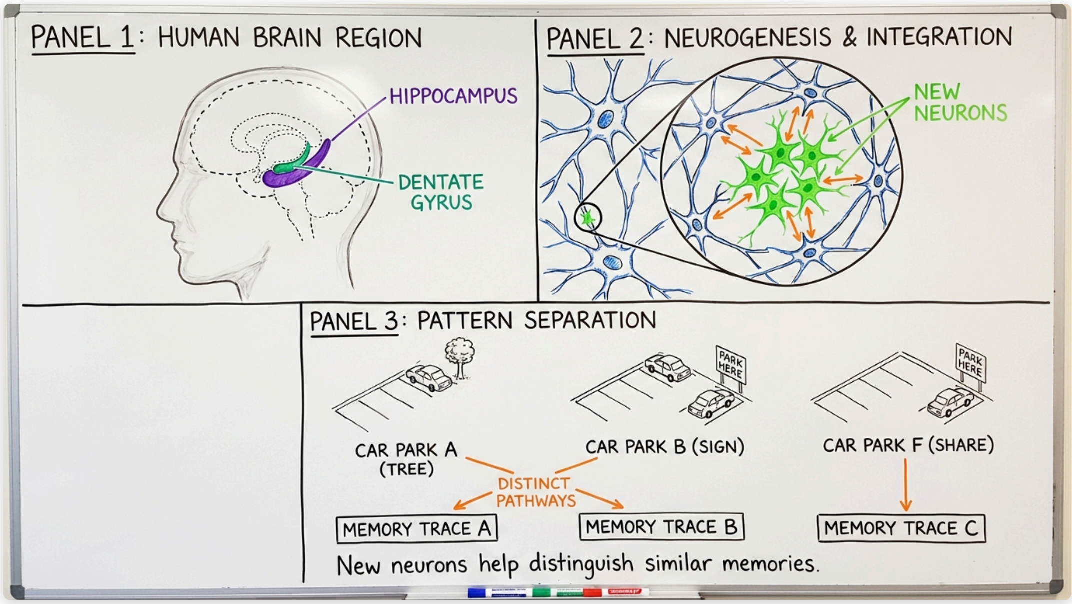


- Here are 4 main points from the text:
- The language a baby hears physically shapes how th processes sounds.
- Music heard before age seven influences a person's develop perfect pitch.
- Early childhood experiences create lasting, physical in the brain's structure.
- Children who learn songlines integrate music, langua space in their brains. This experience permanently o their brains differently.

Full Text

Language and Perfect Pitch Think about what this means. The lar heard as a baby literally shaped how your brain processes sound. music you heard before age seven influenced whether you can ev perfect pitch. These aren't just memories—they're architectural c that last a lifetime. Indigenous Australian cultures use songlines— maps of the landscape—to navigate thousands of miles of territor learn these songs during the critical period for both language anc navigation, creating neural representations that integrate music, l and space in ways that would be impossible to achieve as an adul brains are literally organized differently because of childhood exp

Adult Neurogenesis

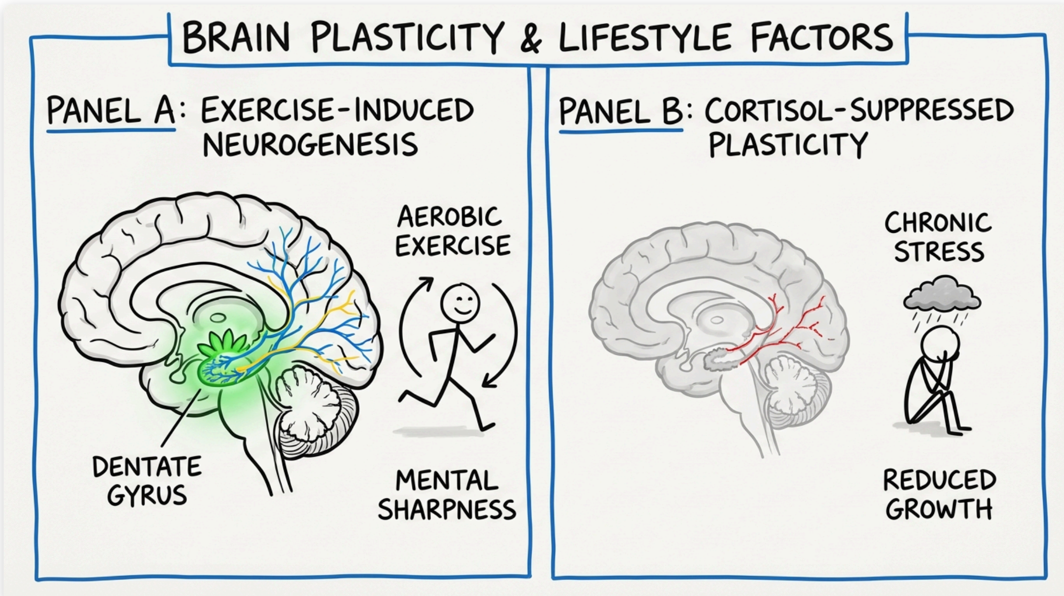


- Main Points:
- The adult human brain creates about 2,000 new neu every day.
- These new neurons develop in the hippocampus and the brain's existing circuits.
- New adult neurons are more excitable, more adaptab help distinguish between similar memories.

Full Text

Language and Perfect Pitch Adult Neurogenesis: The Brain That K Growing For most of the 20th century, neuroscience dogma held brains don't generate new neurons. Santiago Ramón y Cajal hims "In adult centers, the nerve paths are something fixed, ended, im This dogma died in the 1990s when researchers discovered that t human brain produces about 2000 new neurons every day in the gyrus of the hippocampus. These aren't replacement neurons filli dead cells—they're additional neurons integrating into existing cir Young adult neurons have unique properties: they're more excitat plastic, and particularly good at pattern separation—distinguishin similar memories. When you remember where you parked today v yesterday, newly born neurons help keep those similar memories

Exercise Neurogenesis

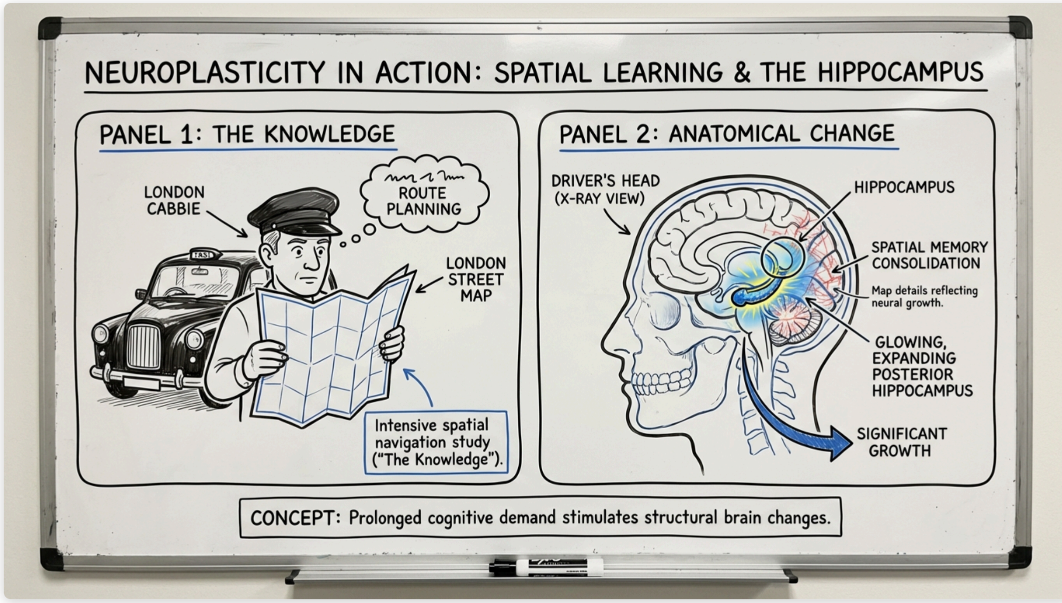


- Here are 3 main points from the text:
- Regular exercise helps your brain grow new cells. Th cells make your mind sharper and improve your mem
- Long-term stress reduces the growth of new brain ce damages memory and can create more stress.
- Many antidepressant medications help new brain cel again. This process aids in treating conditions like de

Full Text

Language and Perfect Pitch Physical exercise doubles the rate of neurogenesis. When mice run on wheels, their dentate gyrus bloc new neurons. This isn't just correlation—the new neurons are nec the cognitive benefits of exercise. Block neurogenesis pharmacol and exercise no longer improves memory. This is why that mornin makes you mentally sharper—you're literally growing new brain ce Chronic stress has the opposite effect. Cortisol, the stress hormo suppresses neurogenesis almost completely. This creates a viciou stress impairs memory, which creates more stress, which further suppresses neurogenesis. Depression is associated with reduced hippocampal volume, partly due to decreased neurogenesis. Man antidepressants, including SSRIs, work in part by restoring neuro they don't just change chemical balances, they restart brain grow

London Taxi Brain

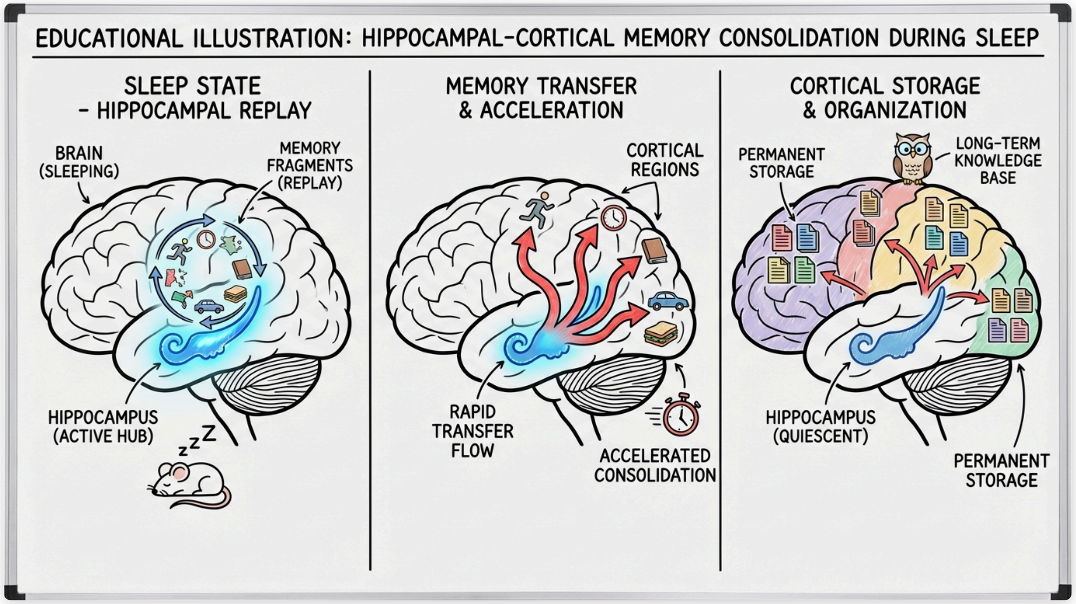


- Here are 4 main points from the text:
- Learning complex navigation, like driving a London ta causes a specific part of the brain to grow.
- Your brain constantly changes and reshapes itself ba the activities you do.
- Practicing mindfulness meditation can increase brair related to memory and decrease areas linked to fear.
- Even brief training, such as juggling, increases brain areas that process visual movement.

Full Text

The London Taxi Driver Study The famous London taxi driver stud that spatial learning physically changes brain structure. Trainee d studying "The Knowledge"—London's 25,000 streets—show prog growth of posterior hippocampus over their 3-4 year training. The increase correlates with navigation performance. Their brains lite expand to accommodate the map of London. Even brief interventi trigger structural changes. Eight weeks of mindfulness meditatior gray matter density in hippocampus and decreases it in amygdala memory while shrinking fear. Two weeks of juggling training incre matter in visual motion areas. Your brain is constantly remodeling what you ask it to do.

Memory Consolidation

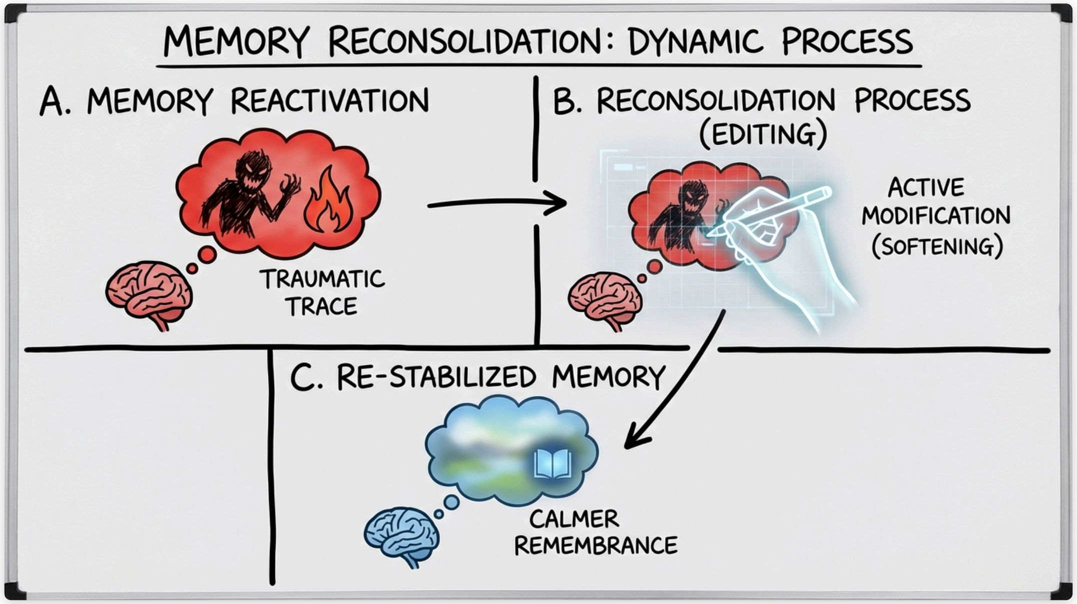


- Memories first form in the hippocampus and then tra the cortex for long-term storage.
- The hippocampus serves as a temporary holding are memories.
- During sleep, your brain quickly replays the day's experiences.
- This rapid replay helps move memories from the hipp to the cortex for permanent storage.

Full Text

The London Taxi Driver Study Memory Consolidation: From Hippo Cortex The memories forming in your hippocampus right now fac journey. If deemed important, they'll gradually transfer to cortex t systems consolidation—a process that can take years. The hippoc like a temporary holding area, keeping memories until cortex is re store them permanently. During sleep, your brain replays the day' experiences at high speed. Sharp-wave ripples in the hippocamp bursts at 150-250 Hz—compress hours of experience into secon replay. Place cells that fired in sequence as you walked through c today will fire in the same sequence tonight, but accelerated 20-f replay drives the gradual transfer to cortical storage.

Memory Rewriting

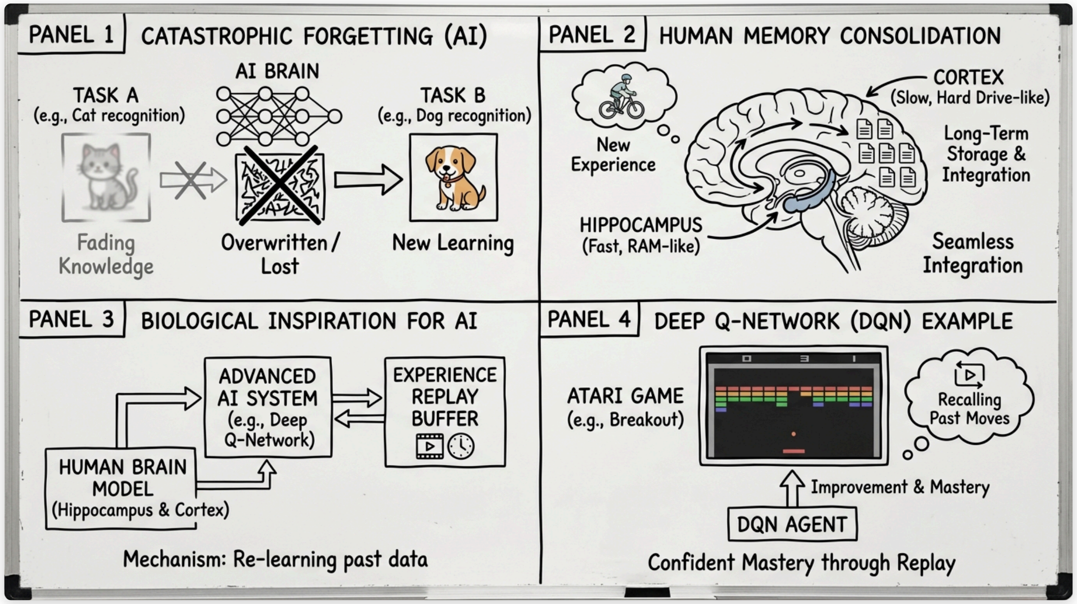


- Main Points:
- Recalling a memory makes it temporarily unstable an change.
- Every time you remember something, you effectively that memory.
- A drug called Propranolol can weaken traumatic men
- Patients take Propranolol during memory recall to rec fear linked to the memory.

Full Text

The London Taxi Driver Study Here's the twist that explains why e testimony is unreliable: reconsolidation. When you recall a memoı becomes temporarily labile again, requiring new protein synthesis restabilize. During this window, the memory can be modified, upd even erased. Every time you remember something, you literally re The memory of your first kiss isn't from your first kiss—it's from tl time you remembered it. This has therapeutic implications. Propra beta-blocker, can weaken traumatic memories if given during reca patients who take propranolol while recounting trauma show redu responses in future recalls. We're not erasing memories—we're e emotional weight during reconsolidation.

Catastrophic Forgetting AI

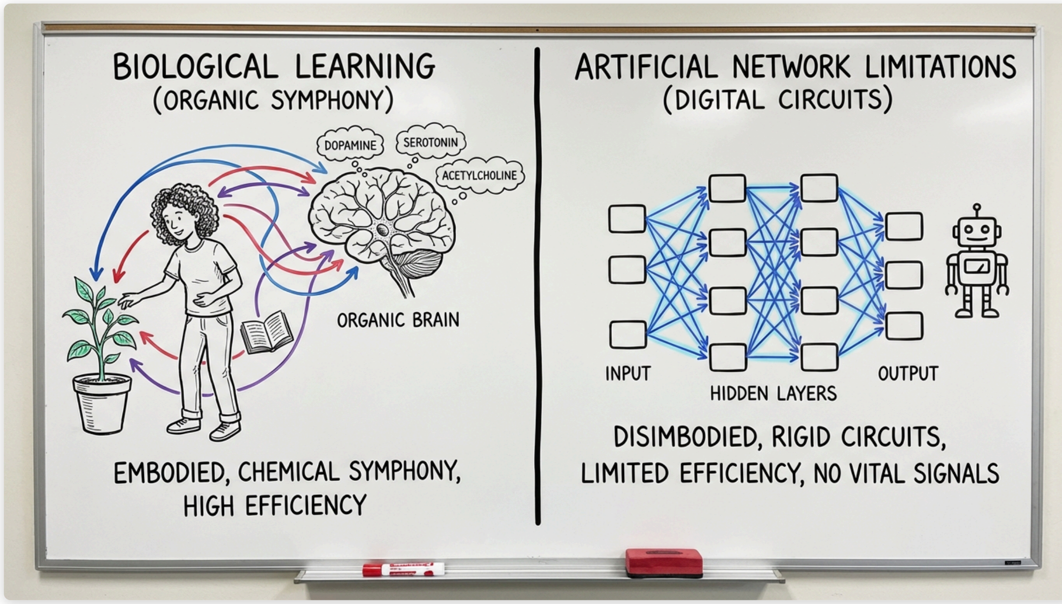


- Here are 4 main points from the text:
- Artificial neural networks experience "catastrophic fo
where they lose old information when learning new ta
- The complementary learning systems theory explains
human brains learn new information without forgettin
material.
- This theory suggests the brain's hippocampus learns
limited memory, while the cortex learns slowly with v
storage capacity.
- DeepMind's Deep Q-Network uses a biological meth
"experience replay" to integrate new learning gradua
avoid forgetting.

Full Text

The London Taxi Driver Study Connecting to AI: What Machines S
Do Artificial neural networks face a problem biological networks s
catastrophic forgetting. Train a network on task A, then train it on
and it forgets task A. But you can learn Spanish without forgetting
How? The complementary learning systems theory proposes that
hippocampus and cortex have different learning rates for good re
Hippocampus learns fast but has limited capacity—it's the RAM. C
learns slowly but has vast capacity—it's the hard drive. The slow
learning prevents catastrophic forgetting by gradually interleaving
information with old. DeepMind's Deep Q-Network borrowed this
insight, implementing experience replay similar to hippocampal sh
ripples. The system stores experiences and replays them during t
allowing gradual integration without forgetting. Biology inspired th
algorithm that defeated humans at Atari games.

AI Biological Limits

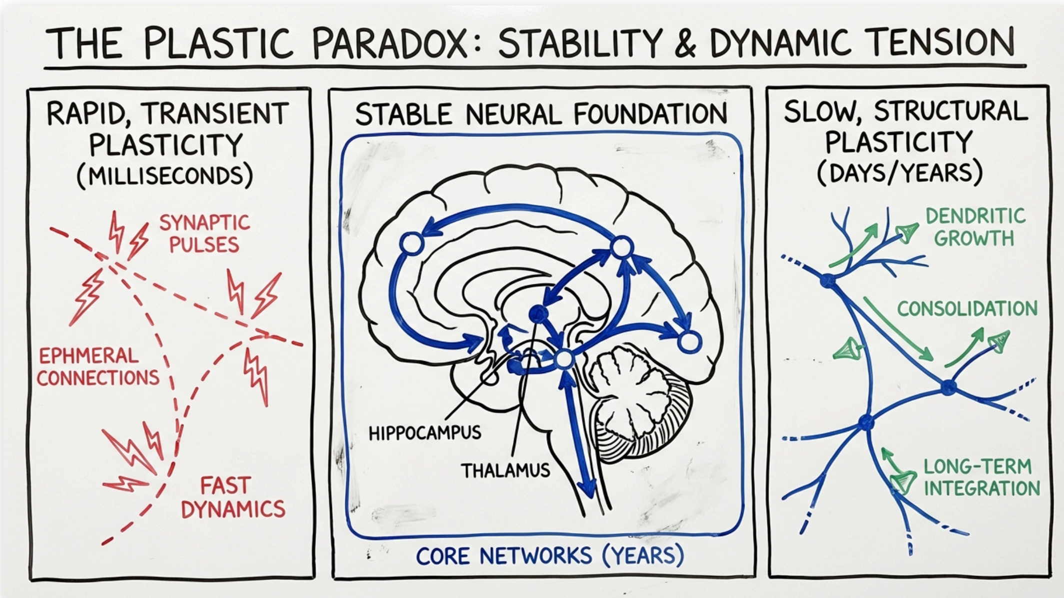


- Here are 4 main points from the text:
- Artificial neural networks use complex gradient calcu for learning. Biological brains learn differently, withou needing these energy-intensive calculations.
- Biological brains use specific chemicals like dopamir serotonin to control how they learn and change. Artif networks do not use these chemical signals.
- Biological learning relies on a physical body interacti the world over time. This physical presence creates t structures important for learning.
- Artificial networks have copied some basic learning r from biology. However, the complete and complex wa learns is still unique.

Full Text

The London Taxi Driver Study But artificial networks still miss cru elements. They lack energy constraints—backpropagation require computing gradients that biology can't access. They lack neurom —dopamine, serotonin, acetylcholine that gate plasticity. Most cri they lack embodiment—the physical presence in the world that pr temporal structure STDP depends on. We've captured some of bi learning principles, but the full symphony remains uniquely biolog

Plastic Paradox

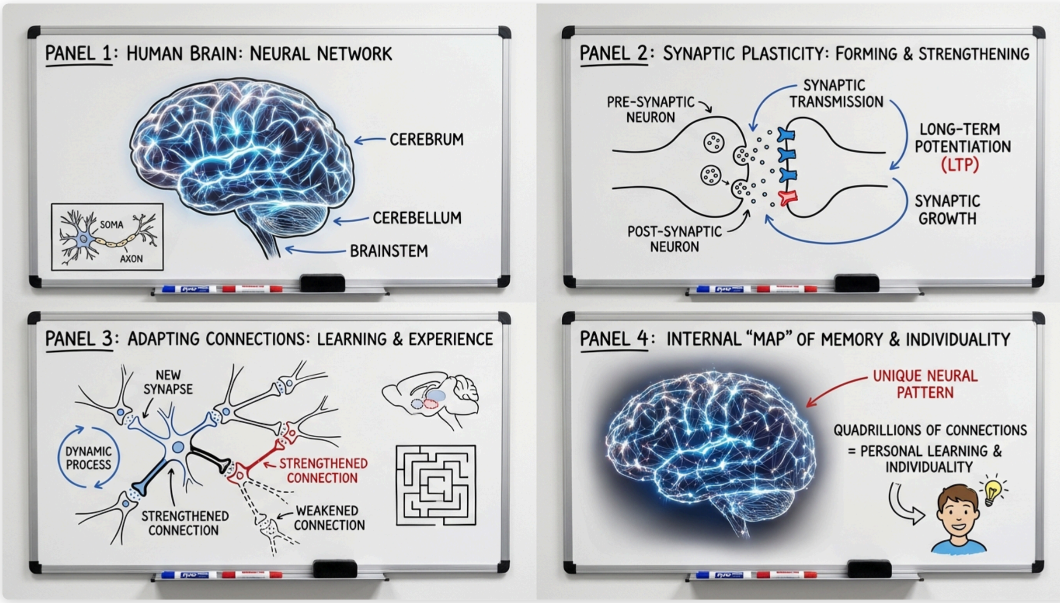


- Here are 4 main points from the text:
- Evolution developed a solution for a complex engine challenge over 600 million years.
- This challenge involves building a system that learns adapts while staying stable and keeping its identity.
- The brain solves this problem using many different mechanisms, not just one.
- These mechanisms operate across various timescale balancing different aspects of change and stability.

Full Text

The London Taxi Driver Study The Plastic Paradox: Engineering C We face an engineering paradox that evolution spent 600 million solving. How do you build a system that can learn without forgetti without losing identity, change while remaining stable? The soluti one mechanism but dozens, operating across different timescales Millisecond spike timing, minute-long calcium dynamics, hour-lon synthesis, day-long structural changes, year-long systems conso each timescale handles different aspects of the stability-plasticity off.

Synaptic Plasticity Disorders

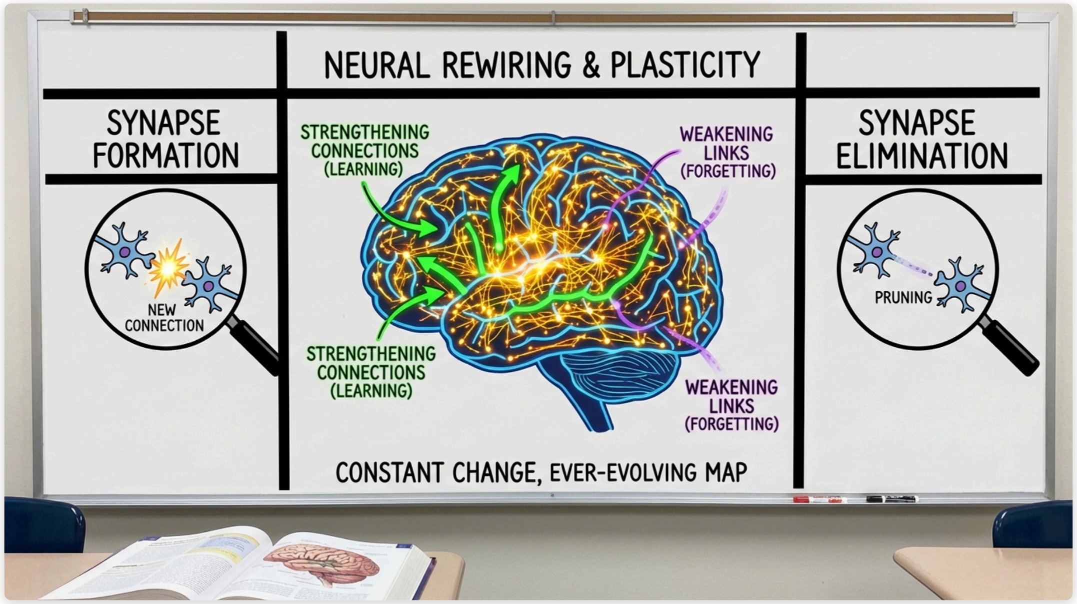


- Here are 5 main points from the text:
- Synaptic plasticity helps us understand brain and me health diseases.
- Many neurological and psychiatric diseases involve p with synaptic plasticity.
- Most psychoactive drugs change synaptic plasticity achieve their effects.
- The human brain contains roughly 1 quadrillion synap each able to change.
- This huge ability for change makes every brain uniqu creates our memories.

Full Text

The London Taxi Driver Study Understanding synaptic plasticity is academic curiosity—it's central to understanding neurological and psychiatric disease. Myasthenia gravis attacks the very machinery synaptic transmission. Parkinson's disrupts the dopamine signals plasticity. Schizophrenia may arise from an imbalance between ex and inhibition, disrupting the delicate choreography of LTP and LT Depression, anxiety, PTSD—all involve disrupted plasticity. Most psychoactive drugs, from antidepressants to psychedelics, work b modulating synaptic plasticity. Consider the numbers: every posts neuron receives about 10,000 connections, each capable of indep plasticity. Multiply that by 86 billion neurons. That's roughly 1 qua synapses, each a potential site of change. This combinatorial exp possibility is what makes every brain unique, every experience pe every memory yours.

Brain Plasticity

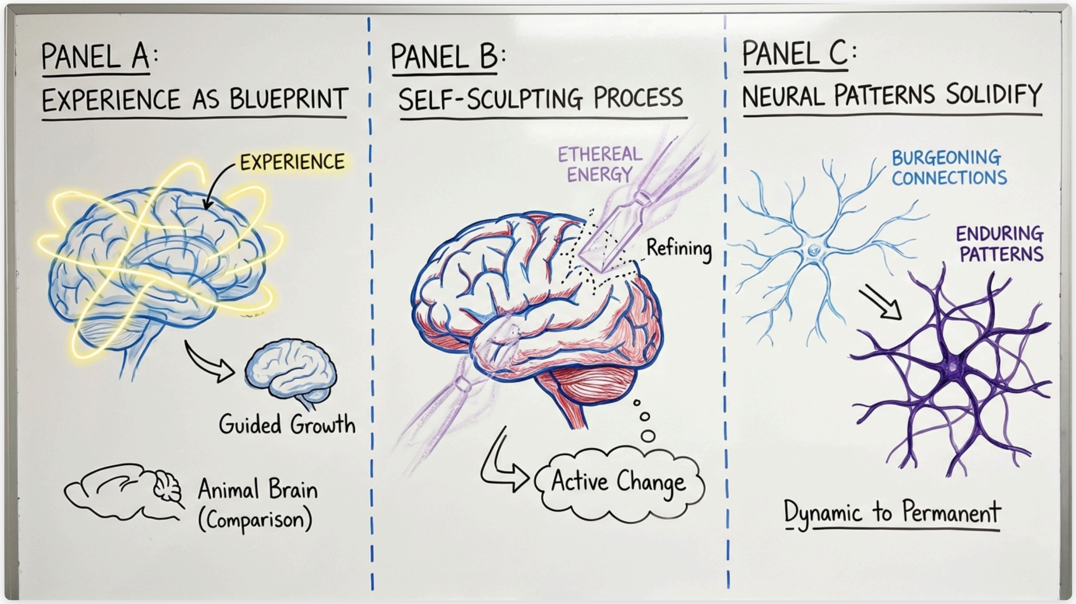


- Here are 4 main points from the text:
- Your brain contains about 100 trillion synapses.
- Synapses in your brain constantly change by strengt weakening, or disappearing. These ongoing changes shape who you become.
- Learning physically rewires your brain by creating ne connections and strengthening existing ones.
- Your brain synthesizes new proteins to make these c permanent. During sleep, your brain consolidates ne learning by replaying patterns.

Full Text

The London Taxi Driver Study Here's the beautiful terror of what w learned today. Your brain contains approximately 100 trillion syna Every moment—right now, as I speak these words—these synapse voting on who you'll become. Some are strengthening, encoding t moment. Others are weakening, letting go of what no longer serve are disappearing entirely, making room for tomorrow's connection didn't just learn about plasticity today—you underwent it. The cor discussed literally rewired your brain. Neurons that had never fire before are now connected. Synapses that were weak this morning strong now. New proteins are being synthesized to lock in these c Tonight, while you sleep, these patterns will replay, transferring fr hippocampus to cortex.

Brain Plasticity

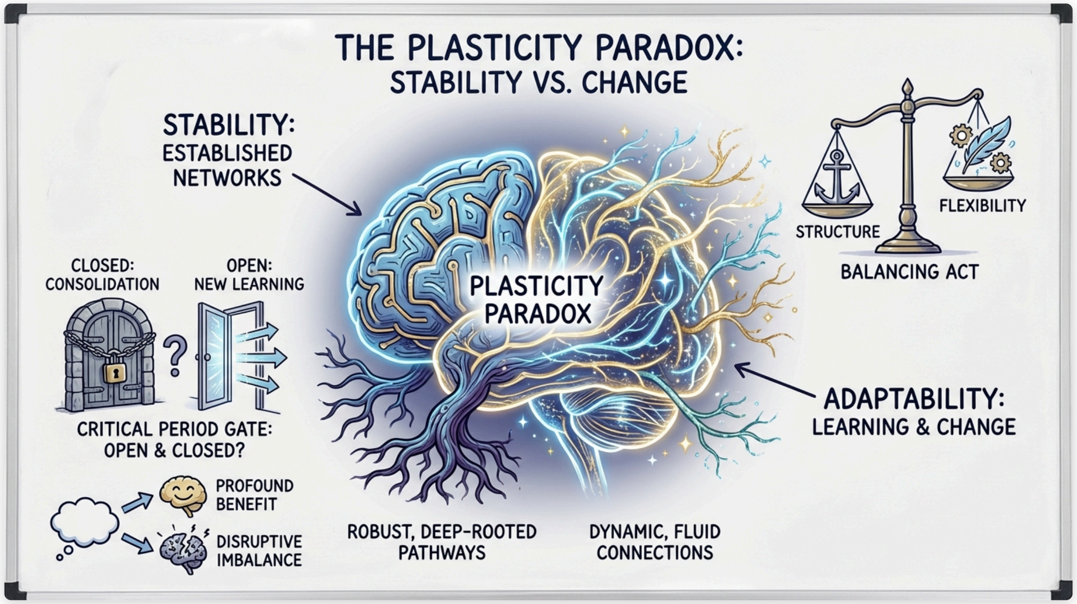


- Here are the main points:
- Our experiences actively shape and change our brai
- The brain can grow and make permanent changes ba new experiences.
- Brain plasticity forms the physical basis for learning, and personal identity.
- This plasticity allows individuals to change and grow maintaining their core self.

Full Text

The London Taxi Driver Study Cajal was right—we are the sculpto own brains. But unlike marble, which only loses material, the brai grow. Unlike clay, which remains soft, the brain can solidify chang any material sculptors have ever worked with, the brain sculpts its experience as both chisel and blueprint. The machinery of plastic calcium influx to protein synthesis, from spine dynamics to syster consolidation—isn't just mechanism. It's the physical basis of lear memory, identity, and change. It's what allows you to be different than you are today, while still remaining you.

Brain Plasticity Paradox

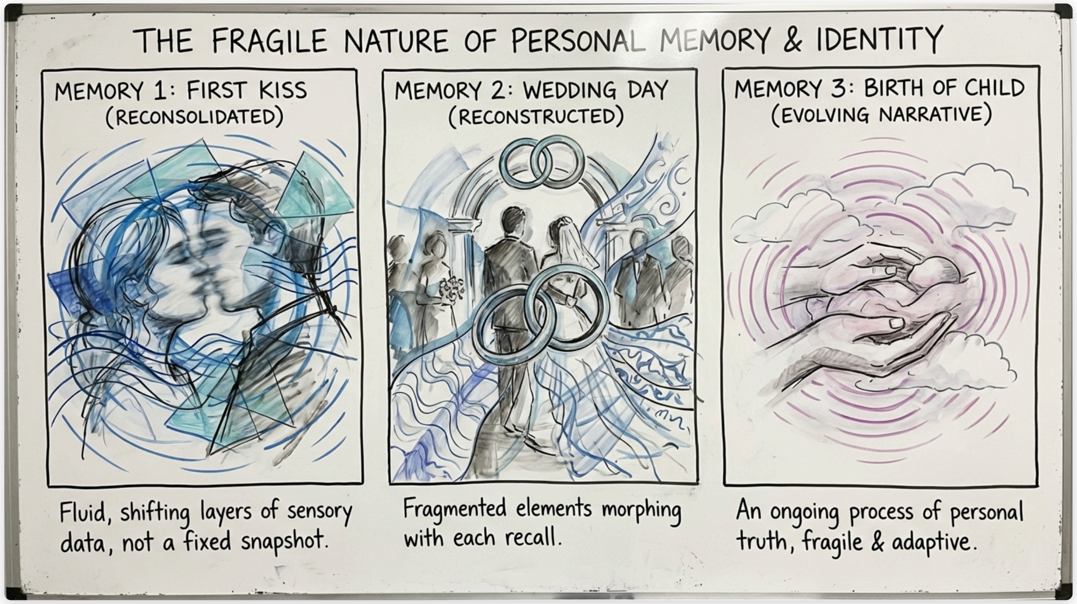


- Here are 4 main points from the text:
- The brain must balance being stable enough to main
identity with being flexible enough to learn new thing
- The nervous system manages this balance using vari
timescales, mechanisms, and different brain regions.
- Critical periods are specific times during developme
the brain undergoes rapid and dramatic reorganizati
- These critical periods close to prevent disruption of t
brain's established circuits.

Full Text

The London Taxi Driver Study Thought Questions for Discussion T questions to spark discussion before your next class: The Plastici Paradox: Your brain must be stable enough to maintain your ident plastic enough to learn. How does the nervous system solve this fundamental tradeoff? Consider the roles of different timescales (milliseconds to years), different mechanisms (functional vs struc different brain regions (hippocampus vs cortex) in your answer. W disorders like autism or schizophrenia represent breakdowns in th balance? The Critical Period Dilemma: Critical periods allow rapid reorganization during development but close to prevent disruptio established circuits. Should we develop drugs to artificially reope periods in adults? What are the potential benefits (treating ambly enhancing language learning) versus risks (destabilizing establish abilities)? How might this change human society if widely availabl

Memory Reconsolidation



- Here are 3 main points from the text:
- Recalling a memory can change it.
- Our most important memories become a mix of diffe
events, not exact copies of the original experience.
- Memory recall challenges our understanding of truth
and legal testimony.

Full Text

The London Taxi Driver Study The Reconsolidation Problem: Ever
recall a memory, you potentially alter it. This means your most ch
memories—first kiss, wedding day, birth of children—may be com
many recall events rather than faithful records of the original exp
this a bug or a feature of the memory system? How does this cha
concepts of truth, identity, and legal testimony?