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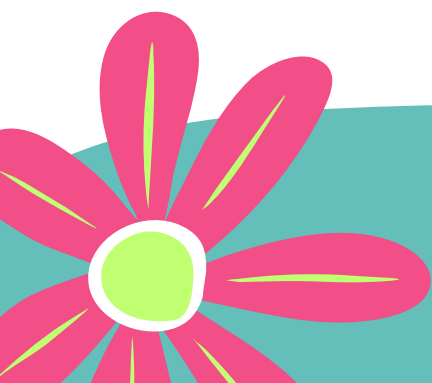


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Neurophysiology Journal

Dr. Mona Rahdar
Assistant Professor of Physiology

Neurophysiology: From a Single Neuron to the Complexity of Human Experience

At every moment, the brain receives, processes, and integrates an enormous amount of information. Seeing a face, hearing a sound, recalling a memory, experiencing pain or emotion, making a decision, enjoying music or art, perceiving beauty, forming a creative idea, and even experiencing an awareness of the self—all depend on the complex and coordinated activity of neural networks. But how does the electrical and chemical activity of neurons give rise to perception, emotion, meaning, and human experience?

Neurophysiology lies at the heart of our efforts to answer this question. Neurophysiology explores how the nervous system functions—from the activity of ion channels and the generation of action potentials in individual neurons to communication between neurons, the organization of neural circuits, and the dynamics of large-scale brain networks. Neuronal excitability, synaptic plasticity, neural oscillations, and interactions between brain regions are central to this field.

These processes can be studied across multiple scales and through diverse approaches, from patch-clamp and field potential recordings to calcium imaging, optogenetics, cellular and molecular methods, computational sciences, artificial intelligence, and behavioral studies. At the same time, the nervous system operates in continuous interaction with the body and the environment—from the regulation of cardiac and respiratory function and autonomic activity to neuroendocrine signaling, the brain-body axis, pain processing, and neuroimmune interactions.

This broad scope leads neurophysiology to questions that extend beyond the function of an individual cell or circuit: How do we learn and remember? How do emotion, language, decision-making, and creativity emerge from brain activity? And how are experiences such as beauty and consciousness related to neural activity?

Perhaps the journey of neurophysiology begins with the simple question, “How does a neuron work?” Yet its horizon extends to a much larger question: How does the activity of the brain and body, through their interaction with the environment, give rise to the complex and unique experience of being human?

In this sense, neurophysiology is a study of the dynamic language of the brain and body—a language that begins with the movement of ions across a cell membrane, unfolds through neural circuits and networks, and ultimately expresses itself in perception, memory, emotion, cognition, pain, behavior, creativity, and consciousness.



Beginning a Shared Journey

Neurophysiology, the study of nervous system function, is one of the fundamental fields of neuroscience. It lies at the intersection of cells, neural circuits, behavior, and cognition, seeking to address one of science's most complex questions: How does the brain function, and how does its activity shape our experience, behavior, and performance?

The **Neurophysiology Journal** was created with this perspective in mind, with the aim of providing a space for learning, dialogue, and the exchange of knowledge in this field. We hope this publication will be more than a collection of scientific content; rather, we envision it as a dynamic bridge connecting researchers, students, and everyone interested in neurophysiology.

In each issue, alongside highlights of recent scientific discoveries, we will explore neurophysiological concepts and phenomena from different perspectives—from cellular and synaptic mechanisms and neural circuit activity to the relationship between brain function, behavior, and everyday life. Featured research, conversations with distinguished scientists and researchers, emerging methods and technologies, and stories from the history of neuroscience will be other parts of this journey.

This publication is a collective effort. The participation of students, researchers, and faculty members in developing, reviewing, and contributing to its content will be an important part of its identity. We hope this collaboration will not only result in reliable scientific content, but also create opportunities for learning, gaining experience, and developing new ideas. In this inaugural issue, we have sought to

present a diverse glimpse into the broad world of neurophysiology—from recent scientific discoveries and topics such as resilience to stories of science, research highlights, and techniques used to study the nervous system.

Our vision for the Neurophysiology Journal extends beyond publishing individual issues. Over time, we hope it will become a space for scientific dialogue, the exchange of new ideas and research, and connections across generations of researchers—a space that brings neurophysiology closer to society while opening new pathways for learning, collaboration, and research. Ultimately, we hope this publication will grow into a dynamic part of the neurophysiology community—a place where new questions are raised, ideas are shared, experiences are passed on, and every issue opens a window onto what we still do not know about the brain and the nervous system.

Dr. Mona Rahdar

Assistant Professor of Physiology

2026 Events Calendar: Physiology, Pharmacology & Neuroscience



1

6th International & 27th National Congress of Physiology and Pharmacology of Iran

This congress was held from February 4 to 6, 2026, hosted by Mashhad University of Medical Sciences in collaboration with the Iranian Physiological and Pharmacological Society. It is considered one of the country's major scientific gatherings in the fields of physiology, pharmacology, neuroscience, systems physiology, cellular and molecular mechanisms, and biomedical sciences.

2

33rd International Congress of Iranian Neurology and Clinical Electrophysiology

This congress was held from April 28 to May 1, 2026, at the Iran International Conference Center in Tehran. Its scientific program covered a wide range of topics, including general neurology, stroke, epilepsy, movement disorders, neuromuscular diseases, multiple sclerosis, headache, cognitive disorders, dementia, and clinical electrophysiology.

3

3rd National Conference on World Brain Day

This conference was held on July 22, 2026, in Tabriz under the theme "Brain Health for All." The main objectives of the event were to raise public awareness, emphasize equitable access to brain-health services, and strengthen collaboration among universities, specialists, healthcare providers, and the community.

4

19th Congress on Addiction Science

This congress is scheduled to be held from October 21 to 23, 2026, at the Razi Convention Center in Tehran. Its topics include the neuroscience of addiction, psychiatry, pharmacological and non-pharmacological treatments, prevention, mental health, and policymaking. It is considered one of the country's major interdisciplinary events in the field of clinical neuroscience.

Events Awaiting Announcement of Dates

The 42nd Annual Congress of the Iranian Scientific Association of Psychiatrists has been announced, and the final dates of the event will be announced subsequently.

International Events Calendar for 2026: Physiology, Pharmacology & Neuroscience

1 AAN Annual Meeting 2026

This meeting is one of the world's most prestigious gatherings in clinical neurology and includes educational programs, presentations of new research, clinical trial results, and discussions of the latest diagnostic and therapeutic evidence. In 2026, artificial intelligence in clinical decision-making, precision medicine, gene therapies, and the application of biomarkers in neurological diseases were among the topics receiving particular attention.

2 American Physiology Summit 2026

This summit is the American Physiological Society's (APS) flagship annual event and provides a platform for interaction among researchers from various fields of physiology. Its scientific program ranges from basic cellular and molecular studies to translational research and clinical applications, while also providing an opportunity to introduce innovative laboratory technologies and develop interdisciplinary collaborations.

3 FENS Forum 2026

The Forum of the Federation of European Neuroscience Societies (FENS) is the largest neuroscience gathering in Europe and is held every two years. In addition to presenting the latest research findings, the event emphasizes training for young researchers, the development of international collaborations, and the introduction of emerging technologies such as artificial intelligence, optogenetics, advanced imaging, and neuromodulation.

4 OHBM Annual Meeting 2026

OHBM is the most important international event in the fields of brain imaging and computational neuroscience. The meeting plays an important role in advancing methods for analyzing fMRI and diffusion MRI data, connectomics, machine learning, and artificial intelligence in brain imaging, and many global standards in these fields are introduced or updated through this organization.

5 INS World Congress

This congress is one of the world's major events in the field of nervous-system stimulation-based therapies. In addition to deep brain stimulation (DBS), spinal cord stimulation, and vagus nerve stimulation, particular attention in 2026 was devoted to closed-loop neuromodulation, brain-computer interfaces (BCIs), and the application of artificial intelligence to the adjustment of stimulation parameters.

6

Society for Neuroscience 2026

The annual meeting of the Society for Neuroscience (SfN), attended by tens of thousands of researchers from around the world, is considered the largest scientific event in neuroscience. This gathering covers virtually all branches of neuroscience, from cellular and molecular biology, electrophysiology, computational neuroscience, neuro-oncology, imaging, cognitive science, and neurotechnology to translational and clinical research. Some new research findings are presented at the meeting in the form of lectures and posters.

7

Alzheimer's Association International Conference (AAIC 2026)

AAIC is the world's largest specialized gathering focused on Alzheimer's disease and other dementias. In addition to presenting new findings on pathology, genetics, biomarkers, and imaging, the conference plays an important role in introducing clinical trials of new drugs and developing global strategies for prevention and patient care.

8

FEPS-SIF European Congress of Physiology

This congress is one of Europe's major physiology events and brings together researchers working in cellular, systems, cardiovascular, neural, respiratory, metabolic, and exercise physiology. In recent years, particular attention has been given to translational physiology, precision medicine, and the interaction of different body systems in maintaining homeostasis.

RESILIENCE: FROM HOMEOSTASIS TO NEUROPLASTICITY

How does the brain resist stress?

Why is it that some people, after experiencing difficult events—such as grief, illness, or severe psychological distress—manage to bounce back, while others struggle for a long time with the aftermath? The answer can no longer be attributed solely to personality traits. Resilience is one of the most critical mechanisms through which humans adapt to stress and life's challenges. Recent findings in neuroscience demonstrate that resilience arises from a complex interplay between neural networks, the endocrine and immune systems, genetic factors, and the environment [1].

In the past, resilience was largely regarded as a relatively stable psychological trait. However, contemporary research has revealed that it is, in fact, a dynamic and malleable process that evolves throughout life under the influence of experience, learning, lifestyle, and environmental conditions [1]. In other words, resilience does not imply the absence of stress or invulnerability; rather, it refers to the brain and body's capacity to adapt effectively to stressful conditions, maintain proper functioning, and restore equilibrium once the crisis has passed [2].



Neuroscience studies have shown that several factors contribute to resilience, including the coordinated functioning of the hypothalamic–pituitary–adrenal (HPA) axis, the interaction between the hippocampus, amygdala, and prefrontal cortex, neural plasticity, neurotrophic factors, epigenetic modifications, and even the gut–brain axis[1, 3].

In this article, we review the most important neurophysiological mechanisms underlying resilience, drawing on recent neuroscientific findings, and illustrate how the brain can adapt to new conditions in the face of stress.

From Homeostasis to Allostasis and Predictive Regulation: A New Perspective on Resilience

The human body is a dynamic system that continuously adjusts to changes in both its internal and external environments. Fluctuations such as shifts in body temperature, changes in oxygen and nutrient concentrations, physical activity, sensory stimuli, cognitive challenges, and psychological stressors all challenge physiological equilibrium. Despite these ongoing changes, the nervous system organizes appropriate physiological responses by continuously receiving, integrating, and interpreting information, thereby maintaining normal bodily function [3].

For over a century, the concept of homeostasis provided the primary framework for explaining this stability. According to this view, regulatory systems maintain vital variables within a specific range or set point using feedback mechanisms[3]. However, research over the past few decades in neurophysiology has shown that the brain does not merely intervene after equilibrium is disrupted; rather, it can predict future conditions and organize appropriate responses before disturbances occur. This predictive capacity—one of the key features of physiological regulation within the framework of allostasis—is known as predictive regulation, and it transforms the brain's role from that of a passive regulator to an active, forward-looking manager [1, 3, 4].

Within this framework, the brain, in collaboration with the autonomic nervous system, neuroendocrine axes, and other regulatory systems, proactively establishes the conditions necessary for maintaining normal bodily function. Thus, physiological stability does not mean stasis, but rather the outcome of dynamic and ongoing regulation that enables adaptation to changing circumstances [1, 3].

Based on Lipsitz's (2002) physiological perspective and subsequent interpretations of her study, resilience can be described as the ability to maintain stable functioning of physiological systems despite environmental changes and challenges [1, 5].

From this perspective, resilience is not a fixed trait that individuals are born with; rather, it is the result of coordinated interactions among neural, endocrine, and immune systems, along with environmental factors, and it can be strengthened or weakened throughout life [6].

When Cortisol Gets Out of Control

The body's response to stress results from the coordinated activity of interconnected neural and endocrine systems, the most important of which is the hypothalamic–pituitary–adrenal (HPA) axis. This axis plays a central role in adapting to stressful situations and maintaining physiological homeostasis [3, 7].





When the brain perceives a situation as threatening, the hypothalamus releases corticotropin-releasing hormone (CRH), which stimulates the pituitary gland. In response, the pituitary releases adrenocorticotrophic hormone (ACTH), which in turn prompts the adrenal glands to secrete cortisol [3, 7].

Cortisol is one of the body's most important stress hormones. In the short term, it plays a vital role in survival by increasing the availability of energy resources, regulating immune system activity, and preparing the body to respond appropriately to challenging situations. However, when the stress response remains activated for prolonged periods, chronically elevated cortisol levels can have detrimental effects, including impaired cognitive function, reduced neural plasticity, and damage to hippocampal neurons [7].

Recent research suggests that the key difference between resilient and vulnerable individuals lies not in the intensity of the initial stress response, but rather in their ability to terminate this response once the threat has subsided. In resilient individuals, HPA axis activity returns to baseline more rapidly, preventing prolonged cortisol secretion. This characteristic protects the body from the harmful effects of chronic stress exposure [1, 8].

In this context, the precise regulation of glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs) in the brain plays an important role in the timely termination of the stress response. Proper functioning of these receptors modulates HPA axis sensitivity and helps maintain a balance between responding to stress and returning to normal physiological conditions [8]. Therefore, resilience depends not only on the activation of the stress response, but also on the efficiency of

the inhibitory mechanisms that, once a threat has passed, shut down HPA axis activity and restore physiological homeostasis.

Three Key Brain Regions Involved in Resilience

Although the HPA axis plays a central role in the stress response, its regulation cannot occur without the coordinated involvement of a network of brain structures. Among the various regions of the brain, the hippocampus, amygdala, and prefrontal cortex play particularly important roles in the development and maintenance of resilience [3].

The hippocampus, best known for its role in learning and memory, is also one of the brain's major inhibitory centers for the HPA axis. Through negative feedback, it contributes to reducing cortisol secretion after a stressful event has ended. According to Rossouw's neurobiological framework of resilience, hippocampal-prefrontal circuits play a central role in regulating the stress response; subsequent evidence has shown that more efficient connectivity of this circuit is associated with more effective stress control and greater resilience [9].

In contrast, the amygdala is a key brain region involved in detecting and processing emotionally salient stimuli, particularly threatening ones. When an individual encounters a stressor, amygdala activity increases, facilitating the initiation of emotional and physiological responses. However, prolonged exposure to stress can lead to amygdala hyperactivity—a condition associated with heightened sensitivity to threatening stimuli and more intense emotional reactions [10].

Under these circumstances, the prefrontal cortex serves as a major regulatory center. By contributing to decision-making, cognitive appraisal of situations, and emotional regulation, it inhibits amygdala activity and prevents exaggerated emotional responses. The

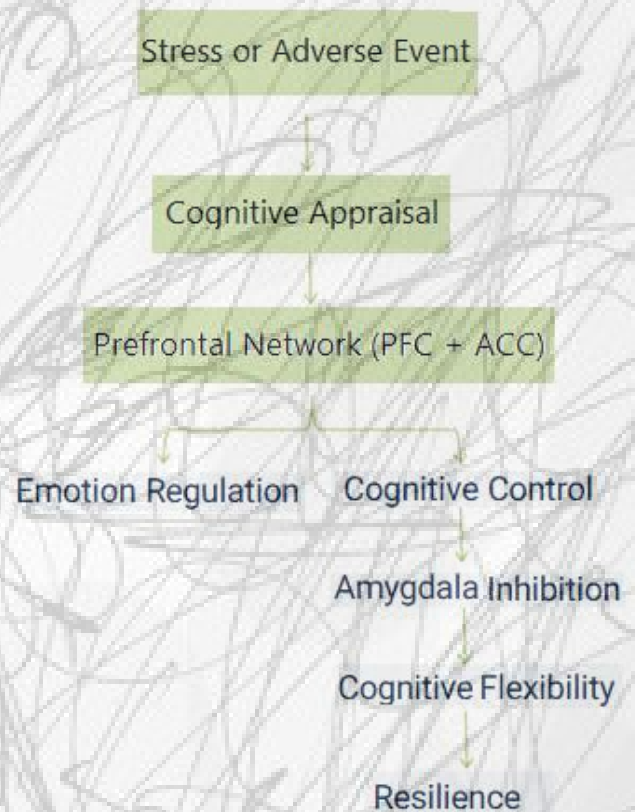
stronger the functional connectivity between the prefrontal cortex and the amygdala, the greater an individual's ability to manage stress, regulate emotions, and select adaptive behavioral responses [3].

In other words, resilience is not the product of a single brain region; rather, it results from the coordinated interaction among these three structures. The hippocampus contributes to the evaluation of past experiences and the inhibition of the HPA axis, the amygdala processes the intensity and significance of threats, and the prefrontal cortex regulates emotional responses through cognitive control. Dysfunction in any of these components, or reduced coordination among them, can impair the ability to adapt to stress and increase the risk of developing disorders such as anxiety, depression, and post-traumatic stress disorder (PTSD) [3, 9].

Can the Brain Become More Resilient?

One of the brain's most remarkable characteristics is its ability to change and adapt in response to new experiences. This property, known as neuroplasticity, allows the brain to strengthen or weaken synaptic connections, form new neural pathways, and reorganize neural networks in response to learning, experience, and environmental changes. Today, neuroplasticity is recognized as one of the most important underlying mechanisms of resilience, as it enables the brain to adapt to new conditions and recover its functioning following stress [3, 9].

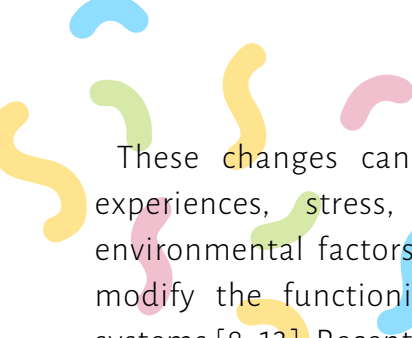
In this process, brain-derived neurotrophic factor (BDNF) plays a key role. This protein supports neuronal survival, promotes the formation of new synapses, and enhances the efficiency of neural communication, thereby facilitating learning, memory, and brain adaptation. Studies have shown that reduced BDNF levels are associated with impaired neuroplasticity and increased vulnerability to stress, whereas higher BDNF levels may enhance the brain's capacity to cope with psychological stress [3, 11].



Another important concept in recent research is cognitive flexibility. This ability allows individuals to shift their perspective when confronted with difficult circumstances, evaluate situations from different viewpoints, and select more adaptive strategies for problem-solving. In other words, resilience depends not only on the intensity of a stressor but also on how the brain interprets and responds to it [12, 13].

A review study by Yao and Hsieh (2019) suggests that this process is primarily mediated by frontal brain networks and top-down cognitive control mechanisms. Through these mechanisms, the prefrontal cortex regulates amygdala activity, reduces the intensity of emotional responses, and facilitates rational and adaptive decision-making. Dysfunction within this network may increase the risk of anxiety, depression, and post-traumatic stress disorder while reducing resilience [13].

In addition to structural and functional changes in the brain, molecular studies have shown that epigenetics also plays an important role in shaping resilience [8]. Epigenetics refers to changes that alter patterns of gene expression without changing the underlying DNA sequence.



These changes can be influenced by life experiences, stress, nutrition, and other environmental factors, and may consequently modify the functioning of stress-regulatory systems [8, 13]. Recent research has shown that changes in the expression of genes such as BDNF, FKBP5, and NR3C1 can alter the sensitivity of the HPA axis and influence an individual's susceptibility or resilience to stress [8]. These findings suggest that life experiences and environmental factors can alter how the brain and stress-response systems function, even without changing the underlying DNA sequence [8, 13].

Therefore, resilience is not simply the product of a fixed brain structure; rather, it emerges from the continuous interaction among experience, learning, molecular changes, and the reorganization of neural networks.

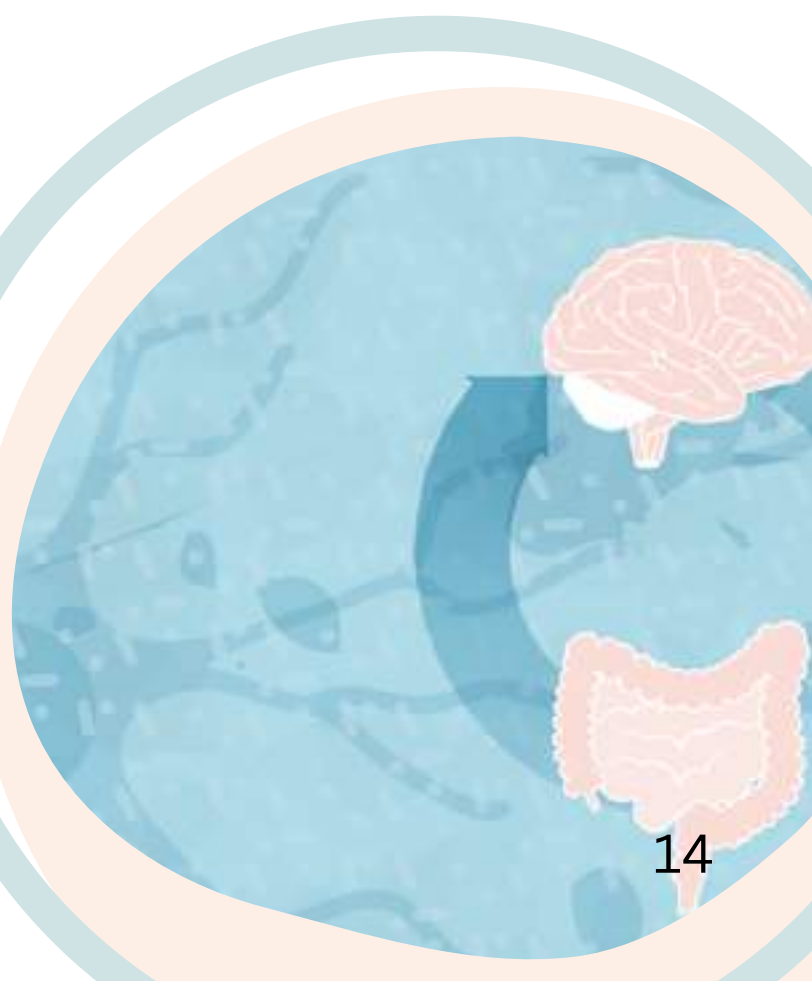
The Immune System and the Gut-Brain Axis: The Hidden Players in Resilience

Until a few years ago, the role of the immune system in resilience received little attention. However, recent findings in neuroscience reveal that the connection between the brain and the immune system is a key factor in regulating stress responses. It is now well established that the brain and immune system are in constant communication through chemical messengers, and any disruption in this interaction can affect mental health and resilience [6, 11].

One of the most significant consequences of chronic stress is increased systemic inflammation and the release of inflammatory cytokines. Elevated levels of these molecules can impair the functioning of the hippocampus and prefrontal cortex, reduce neuroplasticity, and heighten the risk of conditions such as depression and anxiety. Therefore, maintaining a balanced immune system is considered a crucial component of resilience [6, 11].

In recent years, researchers have also turned their attention to the role of the gut-brain axis. This axis represents a complex network of neural, hormonal, immune, and metabolic pathways connecting the gastrointestinal tract and the brain, enabling continuous bidirectional communication between these two organs [6].

Within this framework, the gut microbiome plays a particularly important role. The microorganisms residing in the gut can influence the HPA axis and stress-related neural circuits through the production of metabolites, modulation of immune activity, and effects on neurotransmitter synthesis. As a result, gut microbiome health is now recognized as a factor that can modulate resilience—though this field is still expanding, and further research is needed to fully clarify its underlying mechanisms [6].



Collectively, these findings suggest that resilience does not stem from brain function alone, but rather from the intricate interplay between the nervous system, the immune system, and the gut microbiome. This perspective opens new horizons for understanding the biological foundations of resilience and for developing novel strategies to promote mental well-being.

Neurophysiological Strategies for Enhancing Resilience

One of the most important insights to emerge from neuroscience in recent years is that resilience is not an innate, fixed trait, but a capacity that can be strengthened. Since many of the biological mechanisms underlying resilience are influenced by experience and lifestyle, making targeted changes to daily habits can improve brain function and increase the ability to adapt to stress [1, 2, 6].

Studies have shown that sufficient, high-quality sleep is one of the most critical factors for maintaining brain health and enhancing resilience. During sleep, the brain processes and consolidates new information, reorganizes neural connections, and boosts neuroplasticity by increasing the production of BDNF. Moreover, adequate sleep helps regulate HPA axis activity and mitigates the harmful effects of chronic stress [6, 7].

Regular physical activity is also among the most effective strategies for building resilience. Exercise lowers cortisol levels, promotes neurogenesis in the hippocampus, improves cognitive function, and increases BDNF secretion—all of which enhance the brain's capacity to adapt to stressful conditions. For this reason, consistent physical exercise not only improves physical health but also serves as a powerful intervention for maintaining mental well-being [3, 6, 7].



Healthy nutrition also plays a vital role in sustaining brain function. Adequate intake of essential fatty acids, vitamins, minerals, and antioxidant compounds supports neuronal health, helps maintain a healthy gut microbiome, and reduces chronic inflammation—all factors that contribute to regulating the stress response [6, 11].

In addition to biological factors, supportive social relationships are among the most important contributors to resilience. Having a network of family, friends, or supportive communities can buffer the impact of stress and facilitate psychological adaptation [2, 12]. Furthermore, research has demonstrated that mindfulness practices and psychotherapy—particularly approaches grounded in neuroscience—can enhance resilience by strengthening prefrontal cortex function and improving amygdala regulation, thereby increasing emotional control and adaptive responses to stress. These interventions leverage the brain's neuroplastic capacity to reshape neural networks and reinforce resilience [1, 6, 12].

Thus, enhancing resilience is not limited to treating illness; it can also be achieved through lifestyle modifications, maintaining brain health, and strengthening the body's natural adaptive mechanisms.

Conclusion

Modern neuroscience reveals that resilience emerges from the coordinated interaction of a complex network involving the nervous, endocrine, and immune systems, along with various molecular factors. This capacity is not a static personality trait, but a dynamic, malleable process that evolves throughout life in response to experience, learning, environment, and lifestyle.

Efficient regulation of the HPA axis, proper functioning of the hippocampus, amygdala, and prefrontal cortex, preservation of neuroplasticity, activity of neurotrophic factors such as BDNF, epigenetic changes, and the interplay of the gut-brain axis all contribute to adaptive stress responses.

Understanding these mechanisms underscores that the brain is not a static

organ, but a dynamic and adaptable one, capable of reorganizing its neural networks in response to life experiences. This plasticity paves the way for designing effective interventions aimed at preventing psychiatric disorders, promoting brain health, and enhancing overall quality of life.

Ultimately, perhaps the most important message from neuroscience about resilience is this: the human brain retains its capacity for learning, adaptation, and self-renewal throughout the entire lifespan. Therefore, while stress is an unavoidable part of life, the way the brain responds to it is, to a large extent, teachable, trainable, and improvable.

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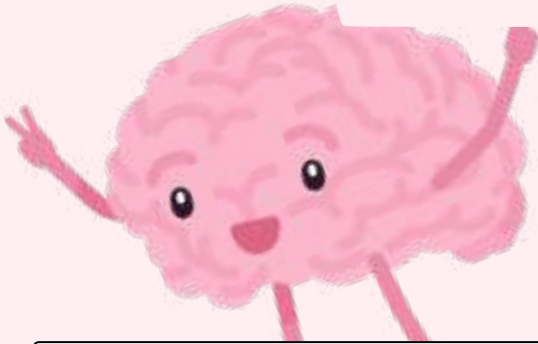
NEUROPHYSIOLOGY OF EMPATHY AND THE HELPING PARADOX

WHY DOES THE BRAIN MOVE TOWARD ANOTHER'S PAIN IN A CRISIS, RATHER THAN FLEE?

In the heart of every large-scale crisis—where safety and peace are snatched from people's lives in the blink of an eye—two groups of reactions always emerge side by side. Some, though caught in the very same danger, move without a moment's hesitation toward the voice they hear through the chaos, to offer help. Others, in that same moment, hear that very same voice, but their feet carry them in the opposite direction. Both are human; both stand in the same moment of peril—but their brains have taken two entirely different paths. Why does one stay while the other leaves? The answer lies in four brief stops within the brain—a pathway that neuroscience has recently mapped with increasing precision.



Brain Stations



Stop One: The body reacts before the mind

The first thing that happens in the brain of that helping individual—even before they realize they are making a decision—is an almost automatic reflex. Mirror neurons, a group of nerve cells in the premotor cortex, "simulate" another person's behavior and state in our own minds, much as if we were performing that action ourselves. Seeing someone trapped in the same crisis activates, without any conscious effort, a subtle motor and bodily simulation within us. Recent research calls this stage "physiological mirroring" and considers it the first stop on the path to empathy—before any judgment, before any moral decision, our body reacts first.

Stop Two: When their pain becomes our pain

The next step is deeper. The brain processes another's suffering within the very same network that senses our own physical pain—a network comprising the anterior cingulate cortex (ACC) and the anterior insula [1]. This is known as the "perception–action model" [2]: witnessing another's pain partially recreates that same pain experience within us. This is what is actually happening at a neural level when we say "my heart aches for them"—not merely a metaphor.

But here lies an important caveat: if the brain stops at this stage alone, the result is not help, but rather a paralyzing form of "personal distress"—precisely what drives that second person, instead of staying, to flee. Bearing witness to pain, without the means to move through it, can itself halt action.



Brain Stations

Stop Three: The boundary between "self" and "other"

What transforms this raw resonance into a tolerable path is the involvement of brain regions that redraw the line between "myself" and "the other"—specifically, the dorsomedial prefrontal cortex and the temporoparietal junction. These areas remind the brain: "This pain is theirs, not mine." Without this cognitive step, emotional empathy alone can become overwhelming.

Interestingly, a recent in Frontiers in Human Neuroscience articulates the process as a perceptual process: from physiological mirroring, to affective response, to cognitive understanding, and finally to appraisal and decision making [4]. This research proposes that empathy is not just a moral virtue, but as a measurable social-perceptual process that can be traced in the brain of that helping individual.

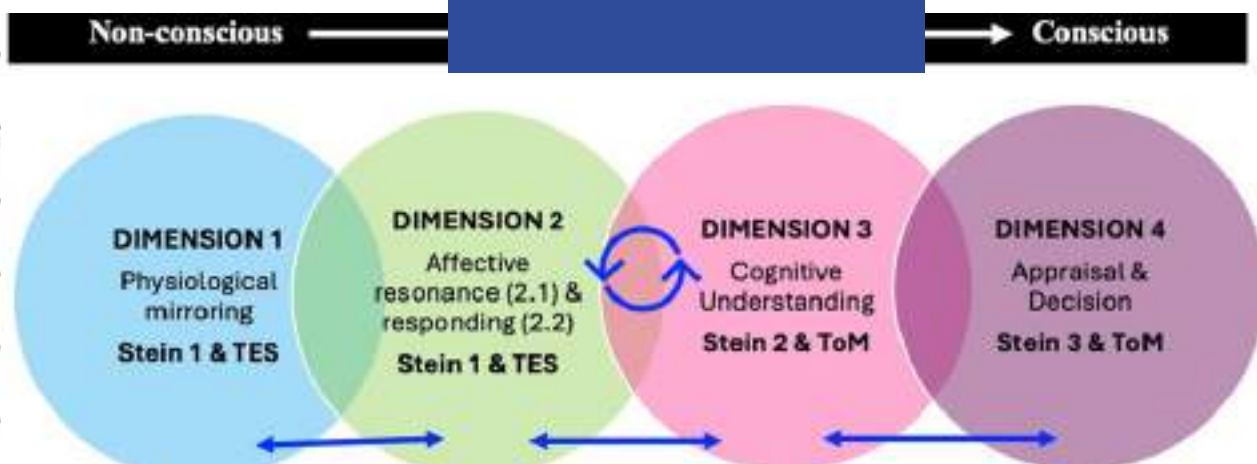


Figure 1: Four stages of empathy as a perceptual process. Integrates Stein (1917), Theory of Embodied Simulation (TES), and Theory of Mind (ToM) across four stages representing increasing levels of conscious awareness.



Stop Four: The reward the brain gives for helping

The final stop is where decision transforms into action—and the brain rewards this choice. The moment someone reaches out to help, dopaminergic reward pathways (the ventral tegmental area and nucleus accumbens) are activated—the same circuitry that lights up with success or pleasure. Simultaneously, the hypothalamus releases oxytocin, a hormone that not only strengthens feelings of connection but also binds directly to receptors in the helper's own amygdala, reducing their anxiety and cortisol levels [3]. Simply put: helping another, biologically speaking, heals the helper as well.

A Horizon for the Future: Is empathy teachable?

These findings raise an important practical question: if empathy follows a four-stage, mappable pathway in the brain, can it be enhanced or even rehabilitated? Recent reviews suggest that efforts involving pharmacological treatments, brain stimulation, and behavioral interventions to enhance or restore empathic function are beginning to emerge, although the effect sizes of these interventions remain moderate and context-dependent [5]. Although this field is still in its infancy, it opens up a promising horizon: perhaps in the future, strengthening empathy circuits could evolve from an ethical aspiration into a genuine clinical target.

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**“THE SECOND BRAIN NO ONE HAD
SEEN: THE HIDDEN NETWORK OF
ASTROCYTES”**

**DISCOVERY OF PLASTIC AND LONG-
RANGE ASTROCYTIC NETWORKS: A
NEW PARADIGM IN BRAIN
COMMUNICATION**

*Astrocytes connect
specific brain
regions through
plastic networks*

Compiled by: Kimia Taghian

A Reconsideration of the Role of Non-Neuronal Cells in the Central Nervous System

In classical neurophysiology, neuronal axons have always been recognized as the main mediators of functional connectivity between different brain regions. However, in recent decades, the role of glial cells—and especially astrocytes—has shifted from mere supportive cells to key players in regulating neural activities. Astrocytes communicate with each other via structures known as gap junctions: membrane channels that connect the cytoplasm of adjacent cells, enabling resource redistribution and the sharing of biochemical signals. Evidence has demonstrated that these networks are essential for memory formation, synaptic plasticity, coordination of neuronal signaling, and even the closure of critical developmental periods. Despite this significance, due to technical limitations in studying intact networks in the living organism, the spatial architecture and functional topology of these networks had remained largely unknown.

In this context, a recent article entitled *Astrocytes connect specific brain regions through plastic networks*

by Melissa L. Cooper and colleagues, published in 2026 in the prestigious journal *Nature*, addresses this gap. The main objective of this research was to develop a novel method for mapping astrocytic networks throughout the brain and to investigate whether astrocytes form only a local network or possess long-range, specific communication systems akin to neuronal networks. The significance of this study lies in its provision of a tool that enable observation of astrocytic connectivity in awake, behaving animals without tissue destruction, as occurs with traditional methods such as slice electrophysiology).

Prior to this study, our knowledge of astrocytic communication was limited to “dye diffusion” in acute brain slices—a method that, because of tissue damage, disrupted local connections. The question remained unanswered whether astrocytes formed a syncytium and an extensive network across the brain, or functioned as distinct sub-networks dedicated to specific regions.

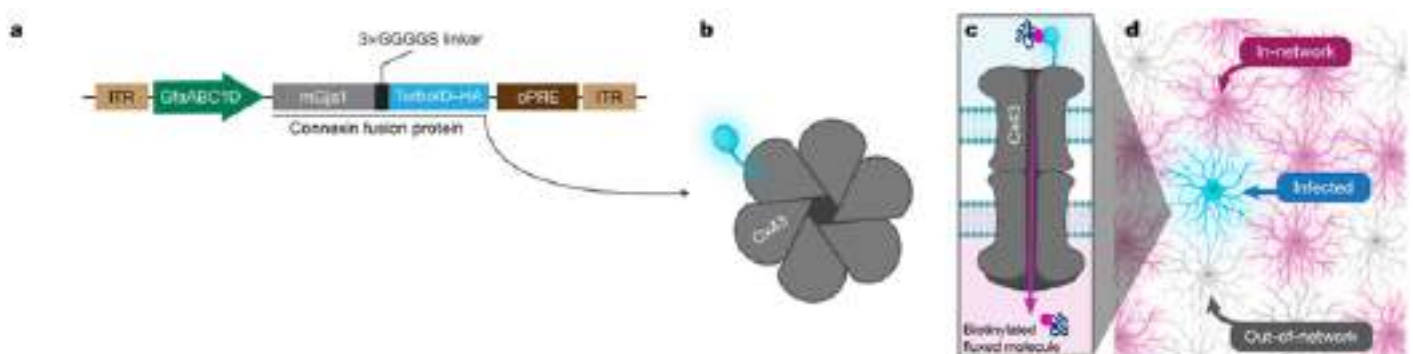


Figure 1 – Visualization of astrocyte connectivity via gap junctions using the astrocytic network tracer. Schematic of the genetic construct of the tracer (Cx43 protein fused to TurboID enzyme). Since each gap junction (connexon) is made up of six connexin subunits, the presence of a single copy of the Cx43–TID fusion protein is sufficient for enzyme localization to the channel. Infected astrocytes label molecules that are transferred through these channels to adjacent, uninfected cells with biotin; thus, three cellular populations can be distinguished: infected cells (HA+/streptavidin+), in-network cells (HA–/streptavidin+), and out-of-network cells (HA–/streptavidin–) (Figure 1 of the main article).

It was also unclear whether the architecture of these networks aligned with neuronal pathways or provided an independent framework for non-neuronal signaling.

Innovation in Tracing: A Tool for Probing the Brain's Hidden Networks

Researchers in this study hypothesized that astrocytes, through plastic networks based on gap junctions, connects distant brain regions in a targeted and organized manner (rather than via random diffusion), and that these networks undergo structural changes in response to environmental alterations.

Despite the importance of astrocytic gap junction networks, studying them has always been challenging because conventional methods such as tissue slice electrophysiology disrupt network connections and, due to tissue damage, introduce experimental artifacts. To overcome these limitations, the research team devised a virus-based approach. The researchers fused the connexin protein Cx43 (the main protein forming gap junctions in astrocytes) with the enzyme TurboID (TID). As a proximity labeling enzyme, TurboID can rapidly biotinylate molecules passing through gap junction channels. Using this labeling, the movement of molecules between astrocytes connected by gap junctions became traceable (Figure 1). The study's results showed that astrocytic networks are spread throughout the mouse brain and molecules diffuse across this interconnected network via gap junctions. However, contrary to previous assumptions, this diffusion is not random.

- The researchers found that multiple networks selectively connect specific brain regions and do not pass through others. For example, the connections and network pattern of astrocytes in the motor cortex were entirely specific to that region; likewise, the hypothalamic network had a distinct set of connections and organization (Figure 2).
- Some networks were restricted to a single region, but long-range networks robustly linked

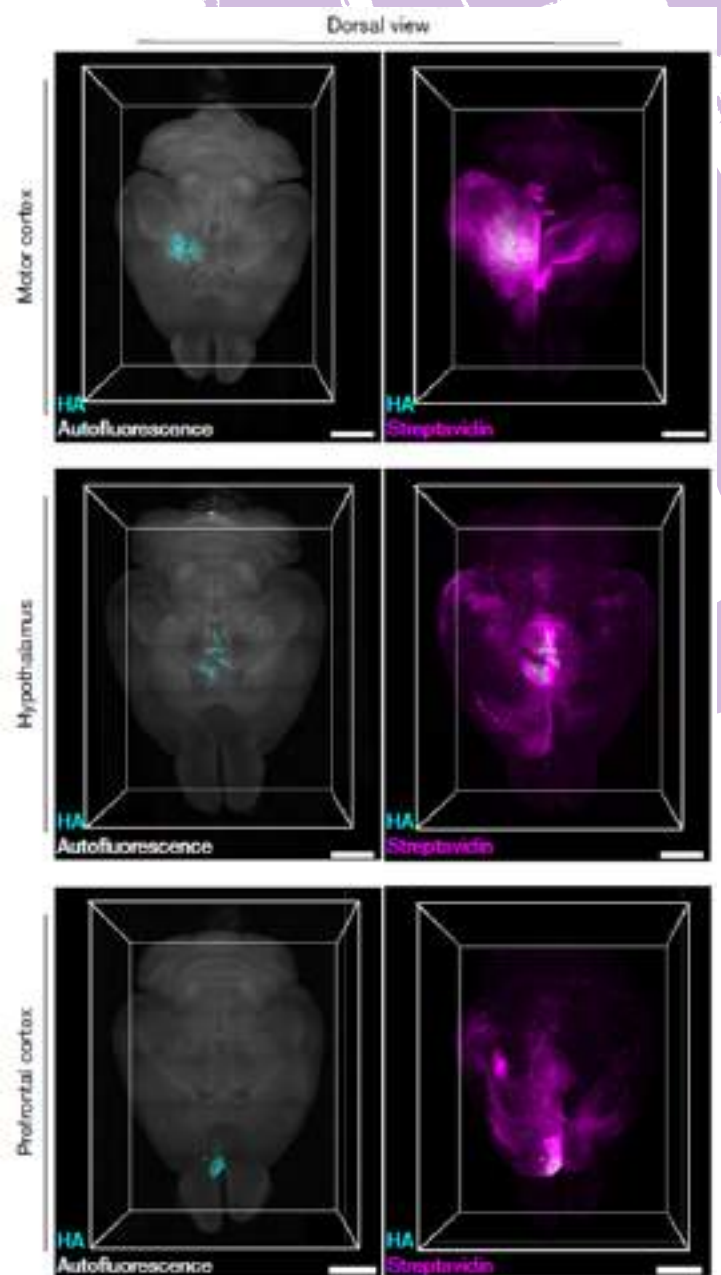


Figure 2 – Multiple astrocytic networks with different sizes and organizations span the mouse brain. Three-dimensional renderings of brains infected with the network tracer in the motor cortex (top row), hypothalamus (middle row), or prefrontal cortex (bottom row), imaged using light-sheet microscopy. Each sample is shown in two images: first, the infected area (HA label, cyan) amid tissue autofluorescence (gray), and then the same area within the astrocytic network labeled with streptavidin (magenta) radiating from that point. (Taken from Figure 2 of the main article.)

- multiple areas across both hemispheres. This finding—that astrocytes in one hemisphere are directly networked with their counterparts in the opposite hemisphere—was among the most important results of the study.
- In a particularly notable part of the experiment, the researchers trimmed the whiskers of mice (Sensory deprivation) and observed that the astrocyte network in the barrel cortex became significantly smaller. This indicated that astrocytic networks, like neurons, are capable of plasticity and undergo remodeling in adulthood (Figure 3).
- Although neuronal and astrocytic networks sometimes overlapped, the architecture of astrocyte networks was often distinct from known neuronal pathways, indicating an independent communication system in the brain.

The findings of Cooper et al. represent a revolution in our understanding of brain architecture; the fact that astrocytic networks can link distant regions across hemispheres shows that our brains do not contain only a “neural network,” but also a parallel, non-neuronal communication system that dynamically reorganizes in response to environmental experiences (such as sensory deprivation).

Innovations and Strengths of the Study

This study introduced several fundamental innovations:

First, the astrocytic network tracer tool made it possible for the first time to trace molecular flux—not just the physical presence of proteins.

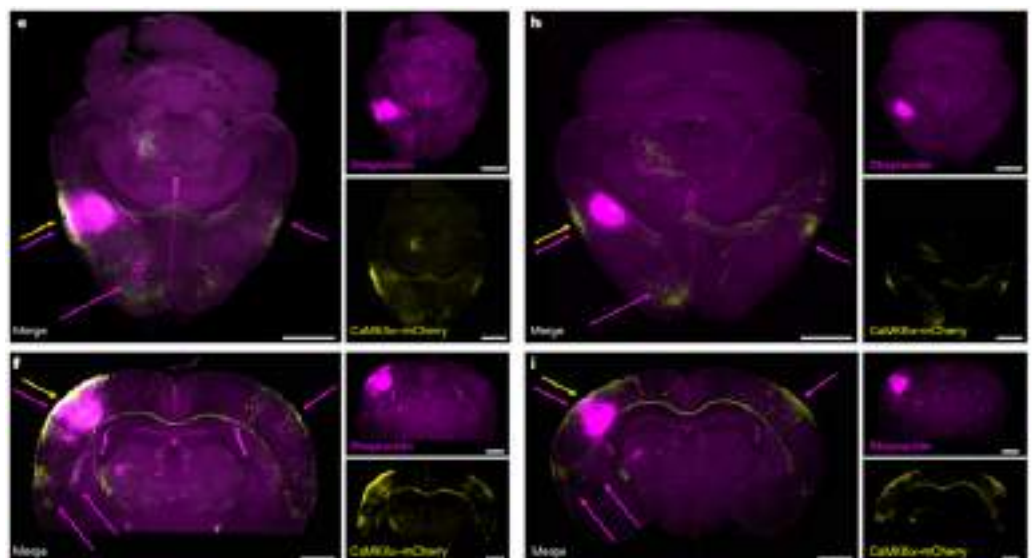
Second, combining this method with whole-brain tissue clearing (not CLARITY, but a solvent-based technique) provided a comprehensive and three-dimensional view that was previously impossible.

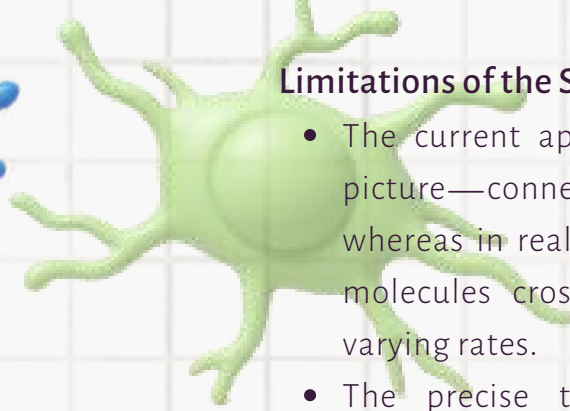
Third, demonstrating glial network plasticity in response to sensory experience changed our perspective on non-neuronal cell dynamics.

Significance of Findings and Conclusion

The findings of Cooper et al. challenge the prevailing “neuron-centric” paradigm: in addition to its neural network, the brain also possesses a parallel, dynamic layer of astrocytic connectivity. These networks likely redistribute vital resources, including antioxidants like glutathione and energy sources like phosphocreatine, from less active regions to those with greater demand; moreover, biotin labeling in neuronal populations indicates that direct astrocyte–neuron communication via gap junctions may be more common than previously thought.

Figure 3 – Astrocytic networks are plastic and differ from neuronal networks. Virtual horizontal (e) and coronal (f) sections provide a detailed view of connection patterns between specific brain regions. Magenta arrows indicate regions where astrocyte connectivity changed following unilateral whisker trimming; yellow arrows indicate the reduction of neuronal dendritic arbors in the same regions after trimming. The images show the brain in an animal with trimmed whiskers, demonstrating the simultaneous shrinkage of the astrocytic (magenta) and neuronal (yellow) networks after whisker trimming (taken from Figure 5 of the main article).





In the field of pathophysiology, this architecture could explain delayed or unexpected astrocyte responses in the contralateral hemisphere in diseases such as stroke and glaucoma, acting as a pathway for the spread of damaging molecules or protective signals.

If astrocytes indeed carry out this logistical role, it appears that disruption of these “hidden networks” could contribute to the progression of diseases like Alzheimer’s, Parkinson’s, and amyotrophic lateral sclerosis (ALS)—a point underscoring that our understanding of brain pathophysiology will remain incomplete without considering glial networks. This framework opens a new avenue for neurodegenerative therapies: instead of directly targeting damaged neurons, we might bolster the brain’s “support and logistics lines.”

This raises an important question: could manipulating this plasticity protect neurons from death during inflammatory storms?

Limitations of the Study

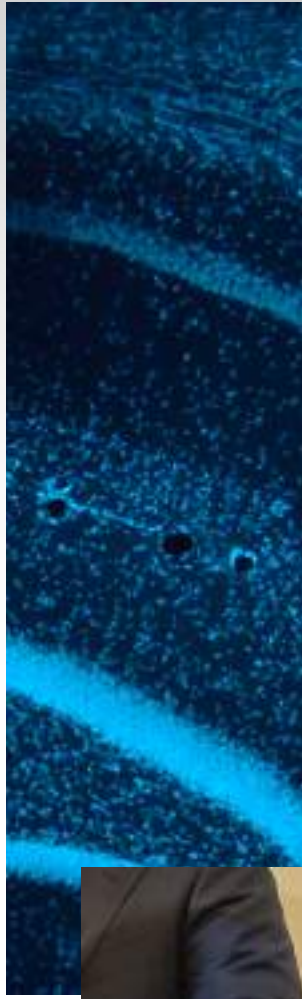
- The current approach offers a binary picture—connected or disconnected—whereas in reality, a wide spectrum of molecules crosses these networks at varying rates.
- The precise temporal dynamics of molecular transfer remain unclear; the observation of certain isolated biotin-labeled astrocytes may reflect cells that were previously connected but have since become uncoupled.
- The possibility that TurboID-mediated biotinylation interferes with other endogenous biotinylation pathways warrants more rigorous control experiments in future studies.
- Definitively confirming the mechanism in complex genetic models remains challenging, since complete ablation of gap junctions can compromise overall cell viability.

Future Directions

Future research avenues include the use of mass spectrometry to precisely identify biotinylated molecules, in order to determine which messengers are exchanged within these networks. Investigating how brain injury, aging, or learning reshape the architecture of these networks could also open new therapeutic targets in neurology.

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IN SEARCH OF LIFE: A SPECIAL CONVERSATION WITH DR. GILA BEHZADI

Interviewers:
Dr. Ali Jafari and Ms. Arefeh Salehi

Dr. Gila Behzadi is a distinguished and seasoned expert in the field of neurophysiology. In this conversation, we invite you to join us on an intimate journey through the twists and turns of her scientific life—from her childhood in Qaemshahr to her years of academic pursuit in France, and the challenges of exploring and sharing knowledge across these past decades. We are honored to have you with us.

Could you please elaborate on your early years and how your interest in education and science first emerged?

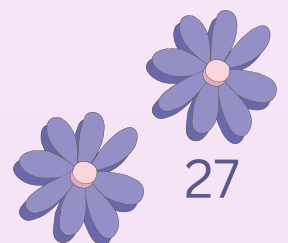
I was born in August 1949 in Qaemshahr, Mazandaran, to a family deeply rooted in culture and academic values. At the age of one, my family relocated to Tehran. Inspired by my mother's profession as a teacher, I developed a growing passion for education. During my studies at Shah Abbas Kabir School and Tabari High School, where I specialized in natural sciences, I was particularly captivated by a course titled “Science of Things”—the precursor to modern experimental sciences. This subject opened a window to a world of discovery for me. My fascination with biological life and the collection of specimens during my teenage years ultimately shaped my professional trajectory.

Could you describe the commencement of your academic career, including your field of study and institution?

Dr. Behzadi: I began my undergraduate studies in Biology at the National University (currently Shahid Beheshti University), specializing in Zoology. During that period, our studies were primarily observational. While we became familiar with various cellular structures, we lacked the technology to visualize neurons directly via microscopy. We could describe their electrical characteristics, but the capability to record neuronal electrical activity was not available. My profound desire to understand the fundamental nature of cells, alongside my commitment to education, became the primary motivation for my advancement into postgraduate studies.

What led you to decide to continue your studies abroad? Did you have a smooth path ahead of you?

Around 1971, the state of higher education in Iran was quite limited; a master's degree in Biology was offered only in Botany, and no doctoral program existed in the field at all. I therefore decided to go abroad. At first, I was awarded a scholarship to Japan, but unfortunately, due to the nepotism and string-pulling that prevailed at the time, I was unable to take advantage of that opportunity. I then set off for England with my brother, who was studying telecommunications engineering there, and devoted myself to improving my English and French along the way. After meeting an Iranian language instructor and benefiting from his guidance, I realized that the cost of studying in England was prohibitively high; on his advice, I decided to pursue a French government scholarship instead, since education there was free of charge.





Could you describe the admission process in France and the competitive nature of the selection?

Dr. Behzadi: Upon my return to Iran, I undertook intensive French language studies at the Institut Français and under private tutelage to qualify for a French scholarship. At that time, language acquisition was challenging due to limited technological resources; communication with foreign institutions was conducted via postal mail, and audio-visual aids were largely unavailable. I participated in the competitive selection exam organized by the Ministry of Science at the Institut Français. Out of 500 applicants, only four scholarships were available for Biology. I ranked among the top 100 and was later among the final 50 candidates selected for an interview. I was ultimately accepted into the University of Bordeaux II and completed my academic French studies at the Faculty of Pharmacy in Montpellier.

What was your experience of living abroad like? Did you ever feel lonely or homesick?

Being away from home is difficult for any student; distance from family, compounded by the lack of effective means of communication back then, was extremely hard. Nevertheless, the French government and universities had carefully

designed cultural, recreational, and pastoral programs to ease the students' sense of nostalgia. This support mitigated feelings of homesickness, leaving me to experience only the physical absence of my family. At that time, the French government provided excellent support for students. Alongside financial aid and insurance coverage, a portion of the program was dedicated to familiarizing students with the country's cultural landscape; this included visits to prominent museums and encouragement to attend cinema and theater performances. These activities, combined with other available amenities, helped enrich the overall experience.

As someone who was educated within the French system, how would you evaluate their approach to student recruitment and investment in education?

Dr. Behzadi: They made substantial investments in education—at times, even exceeding their defense budget. By educating international specialists, they regarded them as ambassadors of both France and the French language.

France also consistently emphasized preserving the authenticity and proper use of its language. Although French may not have achieved the same global reach as English—whose relative simplicity and openness to adopting new vocabulary have contributed to its widespread use—this commitment to linguistic integrity remained a fundamental cultural principle for the French.

After arriving at the University of Bordeaux II, how did your course of study and choice of research direction take shape?

Dr. Behzadi: Upon entering the University of Bordeaux II, I was introduced to the new world of neurobiology. I joined the Department of Behavioral Neurobiology at the Faculty of Medicine, affiliated with INSERM. It immediately recalled the nerve cells I had once longed to observe under a microscope—the very field I had been seeking. Entering this area of study required me to complete supplementary courses at the Faculty of Medicine, including genetics and biochemistry. Genetics, in particular, was very concrete to me at that time: we examined its principles directly and practically through the study of fungi, plants, and animals. What is regrettable today is the removal of precisely these hands-on components from academic curricula—components for which no genuine substitute has yet been found.

What was the system for selecting a supervisor and undertaking research at that time?

Within that system, our academic journey began with the selection of a laboratory and a research supervisor. Once a professor agreed to supervise a student, the formal university enrolment process could proceed, including the student issuance, library, meal-service, and sports-facility cards.

Thereafter, the supervisor determined the appropriate combination of theoretical and practical coursework, in accordance with each student's research direction and academic needs. During those two years of master's study, the laboratory became the center of our lives from morning until evening. Even on days when we attended lectures, we would return to the laboratory immediately afterward. At times, we remained there well into the night; yet, because the residence halls were located on campus, the demands of commuting were largely absent.

What was your supervisor's area of expertise, and what precisely was the subject of your research?

My supervisor was a paediatric neurosurgeon whose research focused on the electrophysiology of the nervous system. My own work involved recording the electrical activity of cerebellar Purkinje neurons in rats. The purpose of our research was to investigate the effects of antidepressant compounds—including thyrotropin-releasing hormone (TRH)—on the excitability of nerve cells. This research was conducted approximately fifty years ago.

Given the technological limitations of that period, how did you record and analyze the data?

Intracellular recordings were obtained using fine glass microelectrodes connected to silver wires. The apparatus translated the cell's electrical activity into an audible signal; by listening to the resulting sounds and observing the corresponding waveforms on an oscilloscope, we could detect the generation of action potentials. As modern computers and digital storage did not exist at the time, we utilized Polaroid cameras mounted on the oscilloscope screen; we would wait for a clear, high-quality signal or response, then capture a photograph of the waveform. Our practical experience was rigorous, involving the use of the stereotaxic apparatus, the recording of skeletal muscle activity, and the meticulous task of manually removing artifacts from the paper charts. We conducted recordings on rhesus macaques, while others in the laboratory worked with the locust ganglia. Ultimately, to validate the recording sites, we transferred the brain samples to the histology department, where we used specialized staining techniques to confirm the precise location. It was through this rigorous process that I developed a deeper and more profound fascination with brain histology.

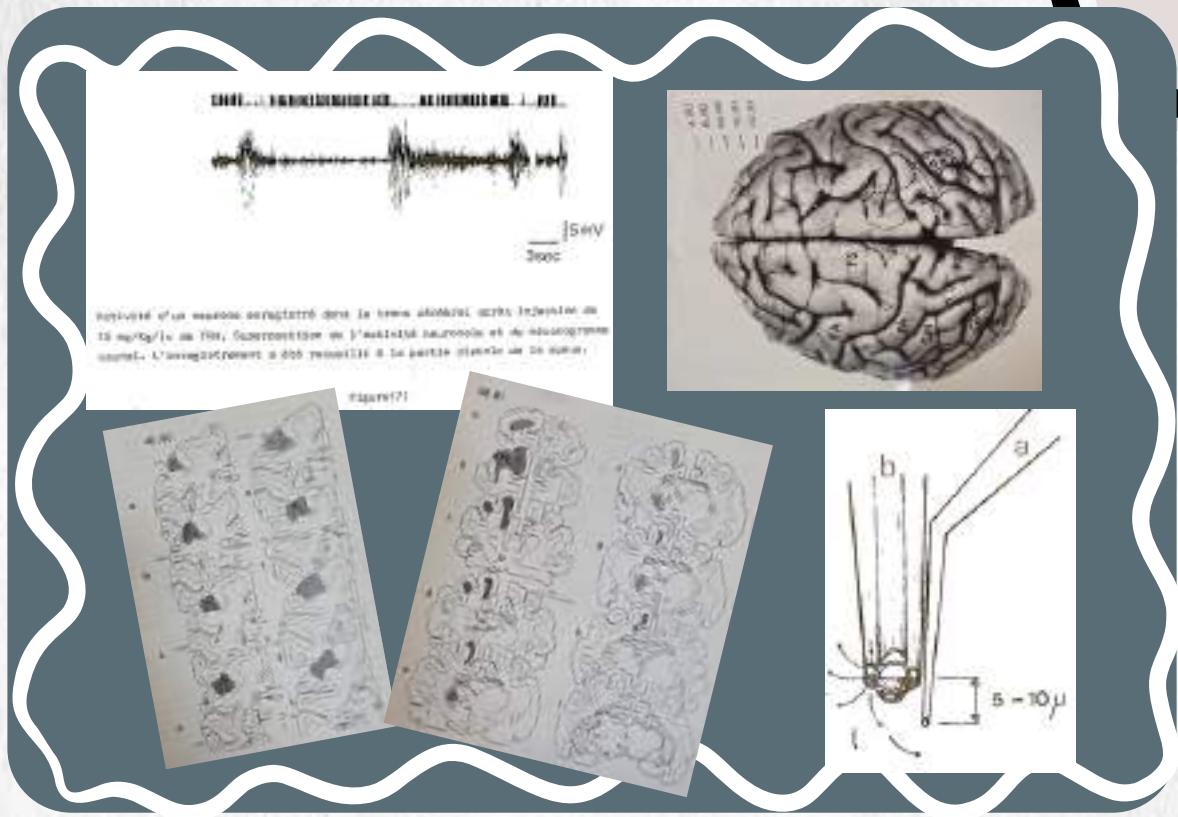
Did you utilize computers in your research during that era?

In those days, computers were colossal machines, often occupying entire rooms. While, back in Iran, I had already gained experience working with punch cards and was proficient in the FORTRAN programming language, in France, our primary recording techniques were still firmly grounded in classical methodologies. It was not until a few years later that early-generation computers began to be integrated into our recording protocols.

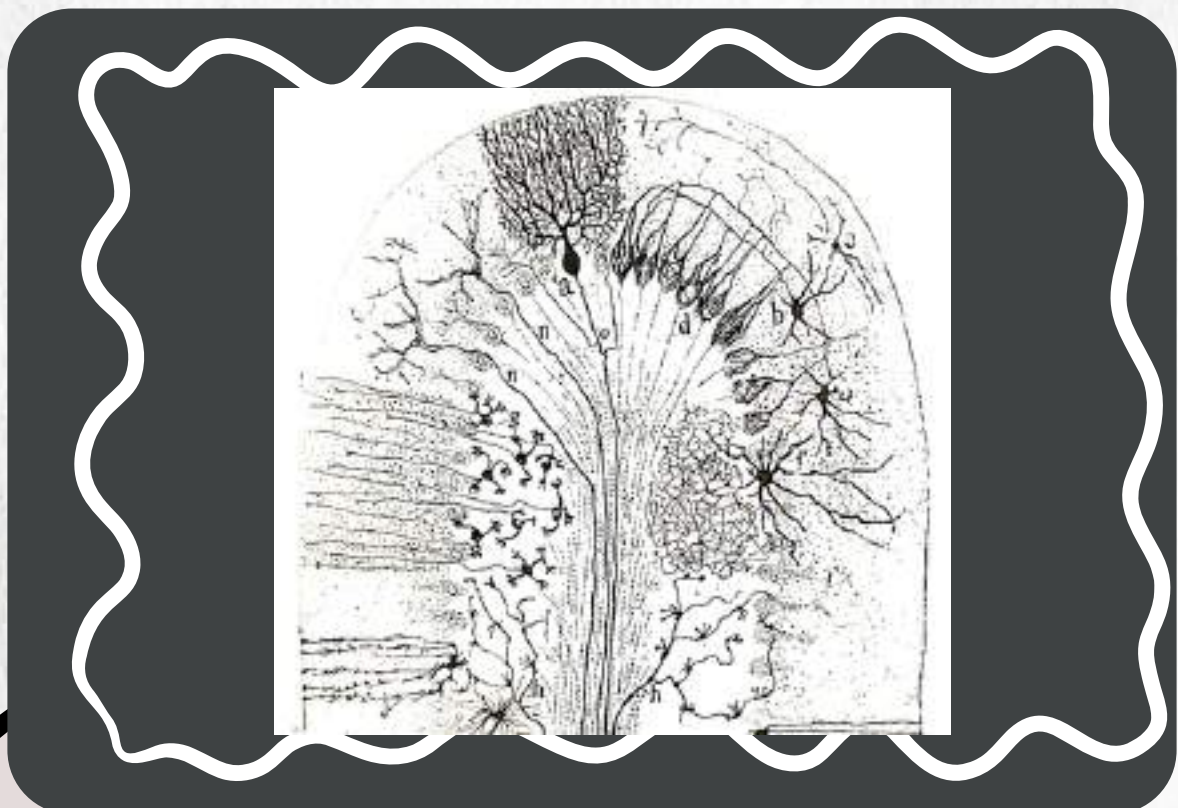
Thesis

Would it be possible to include a few images of your thesis findings for our readers?

Yes, with pleasure.



Dr. Behzadi: I possess a cherished memento of Santiago Ramón y Cajal's work—a depiction of the cerebellar circuitry visualized via the Golgi method—which is widely celebrated as his true masterpiece.





What is your perspective on the trend regarding the volume and length of contemporary theses?

During my time, we prepared our theses with great conciseness, strictly limiting them to three fundamental sections: the Introduction, the Work Undertaken, and the Results—we were, notably, supported by a secretary who handled the transcription. I contend that the current practice of producing excessively voluminous theses is misguided; this is particularly problematic when such documents incorporate material or data that the student has not truly engaged with firsthand, nor been deeply immersed in throughout the research process. The true essence of research lies in the original, practical work that a student undertakes firsthand. This rigorous focus on empirical data—rather than superfluous tangents—was profoundly instructive for me. The thesis committee placed paramount importance on the validity of the results and the data themselves. Indeed, we were even tasked with presenting our experimental findings to medical students enrolled in neurobiology courses; it was an immensely rewarding experience that bridged the gap between our research and classroom education.

Could you share one of the most memorable or defining moments of your research career that remains vivid in your memory?

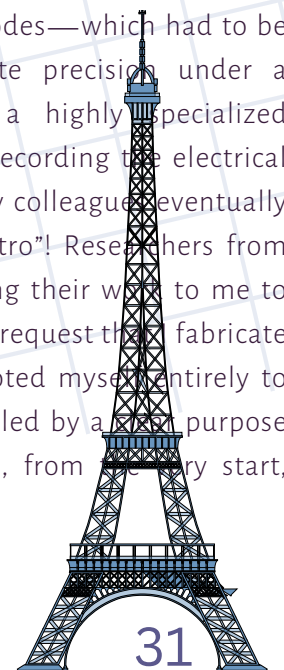
There is a memory from the 1978–79 period that remains etched in my mind. One evening, I successfully managed to record the activity of a Purkinje neuron and captured a flawless Polaroid of the waveform. It was an impeccable representation of the prototypical firing pattern of cerebellar Purkinje cells, distinctly illustrating the regular, rhythmic “on-off” sequence following the application of TRH. To have captured such an ideal result was, for me, a truly unforgettable milestone.

I left the photograph on my desk and retired to the dormitory for the night. The following morning, when I returned to the laboratory, I found all my colleagues gathered, waiting to congratulate me! That particular recording was, for all of us, a significant triumph.

There were times when the neuronal activity would diminish under the influence of the drug. To restore it to its physiological baseline, I would employ a 7-channel multi-pipette technique—each channel measuring only 2 to 4 microns in diameter—to administer glutamate. This intricate, precision-driven work was eventually published as a research paper and was subsequently cited as a reference in authoritative textbooks.

To what extent did your mastery of these techniques establish your reputation within the laboratory?

Working with glass microelectrodes—which had to be pulled and bent with absolute precision under a stereomicroscope—demanded a highly specialized skill set. I became so adept at recording the electrical activity of Purkinje cells that my colleagues eventually dubbed me the “Queen of Electro”! Researchers from other faculties would often bring their work to me to troubleshoot their recordings or request that I fabricate electrodes for them. I had devoted myself entirely to mastering these techniques, fueled by a clear purpose for coming to France that was, from the very start, crystal clear.





How did you proceed with your doctoral studies following your Master's degree?

With the shifting political climate in France following the rise of a Socialist government, my supervisor—a pediatric neurosurgeon—was elected mayor. Coincidentally, the university system had just established its inaugural curriculum in Neuroscience, and I was fortunate to be accepted into the very first doctoral cohort of this program.

The academic structure was quite unique: the university served strictly as the administrative venue for enrollment, while the research itself was carried out under the guidance of investigators affiliated with the CNRS (French National Centre for Scientific Research). The facility housing the CNRS was profoundly evocative; it was situated on the grounds of a vast, historic garden estate—a site once envisioned as a residence for luminaries like Marie Curie, before it was ultimately repurposed for the construction of this prestigious research hub.

I joined the Department of Neurophysiology and the Functional Neuroanatomy research group. My supervisor, Professor Danielle Richet, was a preeminent authority in this field and the author of the Atlas of Baboon Brain Histology. Our research focused on thalamocortical and corticothalamic connectivity in animal models, including monkeys, cats, and rodents. During this tenure, I mastered advanced retrograde tracing techniques, such as the use of Horseradish Peroxidase (HRP) and its conjugate, WGA-HRP, as well as anterograde tracing methods like autoradiography. Notably, we worked with a group of photosensitive epileptic monkeys, whose seizures were specifically triggered by photic stimulation.

The head of our department was, at the time, the pioneering researcher who had discovered this specific form of epilepsy. Ultimately, after successfully defending my doctoral thesis in 1982, I continued within the same research group for a six-year postdoctoral period, which comprised three distinct phases. Furthermore, I spent two years in the Department of Anatomy and Neurobiology in Canada, with the objective of deepening my understanding of the structure of the human brain. It was during this period that I also mastered the techniques of immunohistochemical staining.

How do you reflect on the trajectory of scientific development during that era, and how does it compare to the pathways we see today?

At that time, research centers operated in highly specialized, distinct silos—fields such as neuroendocrinology, electrophysiology, and neurophysiology remained quite separate. Over time, as scientific understanding advanced, these domains converged, eventually giving rise to “Neuroscience” as we define it today. I believe this was a proper, organic evolution. Each scientific discipline must traverse its own developmental trajectory

allowing the corresponding research culture to mature in tandem. If we attempt to take shortcuts or bypass certain foundational stages, we inevitably fail to achieve the necessary efficacy and depth.

What prompted your decision to return permanently to Iran, and how did you find the scientific landscape of the country upon your arrival?

I made an initial attempt to return in 1985, joining the Faculty of Science at the University of Tehran. However, due to the scarcity of essential research infrastructure at the time, I found it necessary to return to France. The turning point came in 1989 when I crossed paths with Dr. Fereshteh Motamedi at a congress in Marseille; she became a staunch advocate of my repatriation. Ultimately, spurred by the urging of my family and friends—and significantly encouraged by Dr. Motamedi—I returned to Iran in the autumn of 1989. Shortly thereafter, I assumed a position in the Department of Physiology at the School of Medicine, which marked the beginning of my academic career there.

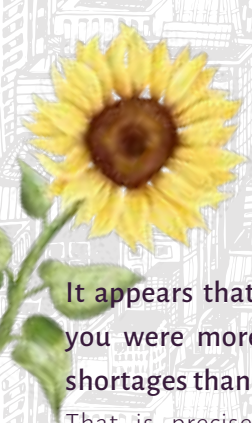
Despite the significant resource constraints at that time, I persevered to establish the tracing techniques within the Department of Physiology. Dr. Mahyar Janahmadi was my very first Master's student. Dr. Saeed Semnian was exceptionally supportive, providing crucial assistance with instrumentation, including the acquisition of a stereotaxic apparatus. In collaboration with Dr. Abbas Foroutan, we successfully set up the perfusion system, and Dr. Abolhassan Ahmadiani generously contributed by importing a Hamilton syringe from Japan. Furthermore, I had personally brought a significant collection of essential equipment and laboratory reagents with me from France.

Among your scientific memories, is there any particular challenge or experience that significantly impacted your perspective on research?

Indeed. Once, while conducting histological tracing studies with Dr. Janahmadi, we initially obtained extraordinary results and were quite elated. However, when we attempted to demonstrate these samples to other faculty members, there was absolutely no trace of staining under the microscope! I spent some time deeply troubled, trying to discern what had gone wrong.

Suddenly, I recalled a conversation with a Japanese colleague who had also been working on tracing techniques; he had lost all his neuronal labeling because he had inadvertently left his samples—which contained peroxidase, a temperature-sensitive protein—exposed to the heat. It struck me instantly that we had encountered the exact same issue. By transferring the samples to the refrigerator, the problem was immediately resolved. This experience served as a poignant reminder that in science, the smallest details are often the deciding factor between a project's success and failure.





It appears that for a significant portion of those years, you were more occupied with overcoming equipment shortages than with the research itself.

That is precisely the case. For instance, we ordered a fluorescence microscope equipped with a monitor, and it took a grueling six to seven years for it to finally reach us in Tehran. Similarly, microscopes and microtomes we ordered were often diverted to other faculties first; we had to engage in persistent advocacy to demonstrate that these instruments were critical for investigating brain “function” within the Department of Physiology.

Unfortunately, the significance of basic sciences was not yet adequately recognized at the time, and the environment for robust scientific discourse remained limited. My training in France had instilled in me the fundamental principle that to truly comprehend function, one must first rigorously elucidate structure. Throughout these challenging years, the academic collaboration and unwavering support of Dr. Janahmadi were a constant source of encouragement for me.

Among the many students you have mentored over the years, is there a particular research project that stands out to you?

Our central aim was to bridge the gap between behavioral performance and neuroanatomical structure. Within the limits of our available infrastructure, we conducted rigorous neuroanatomical tracing studies—for instance, mapping cerebellar pathways or investigating early-stage models of Parkinson’s disease to examine the potential therapeutic effects of Vitamin E on motor behavior. A milestone project was the doctoral thesis of Dr. Mehrdad Roghani, in which we utilized 6-hydroxydopamine (6-OHDA) to induce a Parkinsonian model. It was an immensely challenging and technically demanding endeavor.

Fortunately, we succeeded in publishing the first English-language research article published by our department. Following that success, Dr. Farzaneh Ganji’s project focused on investigating hypothyroidism during embryonic and postnatal development; that study yielded two international publications that garnered commendable feedback from the scientific community. It is worth noting that Dr. Yaghoub Fathollahi had previously published the first international article at Tarbiat Modares University, setting a precedent in our field. All in all, I have mentored approximately thirty graduate students, and it is a profound source of pride for me to see each of them now established and flourishing in their respective academic institutions.

You consistently emphasize the importance of “experience.” Why do you believe a student must navigate the rigorous stages of laboratory work?

The fundamental distinction between histotechnological research and other inquiries in behavioral or electrophysiological techniques lies in the uncertainty; you remain unaware of whether you have obtained a valid result until the entire process has concluded. Today, many private entities perform histological analyses without the requisite scientific depth. However, I firmly believe that true learning cannot occur unless the student personally grapples with every intricacy of the process—from perfusion and sectioning to staining and microscopic examination. When passion and genuine interest are present, these hardships become transformative. I have always preferred to work alongside my students, guiding them step-by-step so that they may truly grasp and internalize the essence of scientific inquiry.

What foundational philosophy has kept you determined throughout such a challenging and tumultuous path?

I have always pursued an “objective understanding” of the subject matter, regardless of the approaches others might take. In my view, many of the challenges we faced stemmed from “not knowing” rather than “not wanting.” It was often a matter of lacking the necessary methodological clarity. Furthermore, cumbersome bureaucracy frequently hindered the timely progress of our work. However, deep passion and conviction are what keep researchers resolute on this path. Truth be told, we still face significant shortcomings in many areas; our research often retains a primarily didactic character, inherited from elsewhere, without being fully adapted or tailored to our own scientific environment.

Human physiology is inextricably linked to one’s environment, social circumstances, and indigenous nutritional heritage. We must cultivate a deeper understanding of our own “indigenous physiology” if we are to effectively address the unique challenges we face. Nevertheless, we have certainly made strides during this time; I have witnessed this firsthand at national congresses, where I observe a great deal of genuine passion and drive among the younger generation.



In your view, what are the primary pitfalls along the scientific path?

Economic instability and the lack of social support systems are undoubtedly significant impediments. Emotional and social encouragement are vital, and the absence of such foundational support often renders the journey unnecessarily arduous. I recall a memory that remains etched in my mind to this day. When I was a master's student living in the women's dormitory, I overheard the dormitory manager collecting feedback from the residents one summer. When the staff member remarked, "I have collected everyone's feedback, except for room 107, because she is not 'French' [referring to my study background/discipline]," the manager replied in a firm, reproachful tone: "Why did you not ask for her input? She is pursuing a Master's degree in Neurobiology; she is an 'academic individual'! Go back and secure her feedback immediately."

When I heard this, I was deeply moved. In that society, regardless of your nationality, you were respected and acknowledged for your scientific integrity and knowledge. The feeling that you had earned a meaningful place in society because of what you knew was profoundly valuable. Another pitfall along the scientific path is the pursuit of status and recognition. For me, there was simply no place for such considerations; they never entered into the equation. If we set aside the pursuit of name and reputation and focus instead on reality, we are able to act with greater strength and conviction. Years later, my students come to recognize the value of the principles I had emphasized to them.

As a professor who has worked with generations of students over the years, what, in your view, are the hallmarks of an "exemplary mentor"?

The criteria for an exemplary mentor may vary across different cultures, but experience has taught me that in our country, a professor must, above all, be "self-sacrificing." A professor is expected to simultaneously embody the roles of teacher, coach, and educator; one must recognize the latent potential in young minds and approach their development with a holistic perspective. Perhaps in other nations, this balance shifts, but here, such a supportive and nurturing outlook is vital if society is to truly benefit from the talents of its youth. A thought

I constantly remind myself of is this: when you move to a foreign land, you adjust your expectations as you acclimate to that society. However, in your own country—because you belong to it—your expectations remain perpetually higher.

Within the realm of research and education, what do you believe are the critical shortcomings that demand serious reform?

I have always treated every student's experience as a lesson and strived to anticipate future challenges. Yet, I am perpetually confronted with new behaviors and evolving expectations. I believe the fundamental issue lies in a lack of "social cohesion" in our academic community. When such cohesion exists, behaviors become more predictable, and scientific advancement proceeds more fluidly. Perhaps we need to mentor students not only in science but also in navigating the broader social landscape effectively.

Curiosity and a drive for innovation are inherent in all students; however, they must be given space for creativity and latitude for trial and error. Unfortunately, pressing concerns—such as employment, housing, and an uncertain future—constrain their capacity for deep reflection and scholarly inquiry. When a student's mind is preoccupied with merely "getting it done quickly and moving on," there remains no room for the arduous, rewarding exploration of the unknown. Furthermore, "grade-centrism" and a preoccupation with hierarchical power are significant blights on our academic culture. We must cultivate a genuine research mindset and a commitment to collaborative teamwork. Above all, a strong, trust-based bond between student and mentor is essential.

One of the most fundamental systemic flaws we face is a profound lack of equity; the system is plagued by an overabundance of exceptions. This undermines the hope that hard work and integrity will lead to merit-based outcomes, and these systemic biases ultimately stifle genuine talent. Perhaps the path of righteousness does not yield immediate dividends, but it fosters far more sustainable results and leads to success that is both deeper and more enduring.





What is your perspective on the current status and future of the field of “neurophysiology”?

Neurophysiology is the science of understanding the human being—a field that will never fade, for all cognitive processes and physiological functions are tethered to the brain. In today’s scientific landscape, our understanding is becoming increasingly granular and precise. I view neurophysiology as a vital network interconnected with all life—from the chemical signaling exchanged between the leaves and

branches of a tree to the reflexive movements of the simplest organisms. As masterfully captured in David Attenborough’s documentaries, all these connections are facets of a vast, integrated whole. If we choose to study and preserve these connections—rather than dismantle them—the opportunities for discovery are boundless. The exploration of the unknown is infinite, ensuring that for the dedicated researcher, there is always profound work to be done.

In clinical fields, basic sciences are sometimes undervalued. What is your perspective on this?

Across all medical specialties, physicians and clinical staff must maintain a profound appreciation for the underlying interconnectedness of physiological systems. Diseases, complex behaviors, and human responses—all ultimately stem from the fundamental principles of neurophysiology. Scientific disciplines should not operate in isolated silos. I have worked in Iran for approximately 35 years, yet I have yet to encounter a structural framework in which diverse departments operate in synchrony toward a unified objective. Research remains largely fragmented and credential-driven. We must foster independent yet synergistic research groups that are truly capable of addressing genuine, real-world clinical needs.

Amidst all these challenges, what kept you from losing heart or giving up?

In truth, the very problems I encountered became the fuel for my perseverance! My response to these hardships was to focus on the changes I could effect, however incremental they might be. I recognized that most of these systemic issues were not born of malice, but rather of a lack of awareness within the broader social culture or a systemic oversight. That realization—that these were solvable issues rooted in misunderstanding—gave me the strength to remain steadfast and continue on my path.

Do you have any books or works of art you would like to recommend to the readers of this journal?

A book that made a profound impression on me during my youth was *Beyond Faces (An Suy-e Chehreha)* by Naser al-Din Sahib al-Zamani; it was an exceptionally thought-provoking work. Regarding cinema, the films we watched in my earlier years possessed a depth and instructive quality that I find increasingly rare today. Works such as *Roots* and *Uncle Tom’s Cabin* left an indelible mark on me, as they starkly and poignantly depicted the history of Western atrocities against Black people. Margaret Mitchell’s *Gone with the Wind*—both the novel and the film adaptation—was also, in its own right, a true masterpiece.



Do you have any advice for students or young faculty members?

In the face of new technologies and the generation that has grown up with them, we should avoid a superficial outlook and instead use these tools to nurture curiosity and improve the quality of life. When we entered university, we loved it deeply and spent the entire day in the department; we regarded it as our duty. Today, that sense of enthusiasm is sometimes less visible, and it often seems that students' presence on campus is driven more by obligation than by genuine interest. Perhaps one reason is the lack of sufficient appeal to stimulate curiosity, a mismatch with the sensibilities of the new generation, and limited freedom to pursue one's preferred path. The shortage of resources has only made matters worse.

Individuals must be empowered to choose paths aligned with their innate aptitudes and personal interests, interests, and they should be actively supported in that pursuit. Such dynamics are what truly cultivate a vibrant and resilient society. Broadening our networks of communication can resolve a myriad of problems—provided these connections are built on collaboration rather than competition, where individuals derive genuine joy from their interactions. Furthermore, exposure to social and psychological sciences is critical; the seeds for this understanding must be sown from early childhood.

I recall that during my master's program, my professor once had to cancel a class due to an urgent surgery. The students—even those from medicine—left the classroom visibly disappointed. That moment spoke volumes: when the value of a goal and the significance of one's academic path are made clear, the internal drive is already there. The educational system must act as a catalyst for these motivations, rather than a force of suppression. These changes will undoubtedly be gradual, but they must be persistent and unwavering.



“Do you have any closing remarks?”

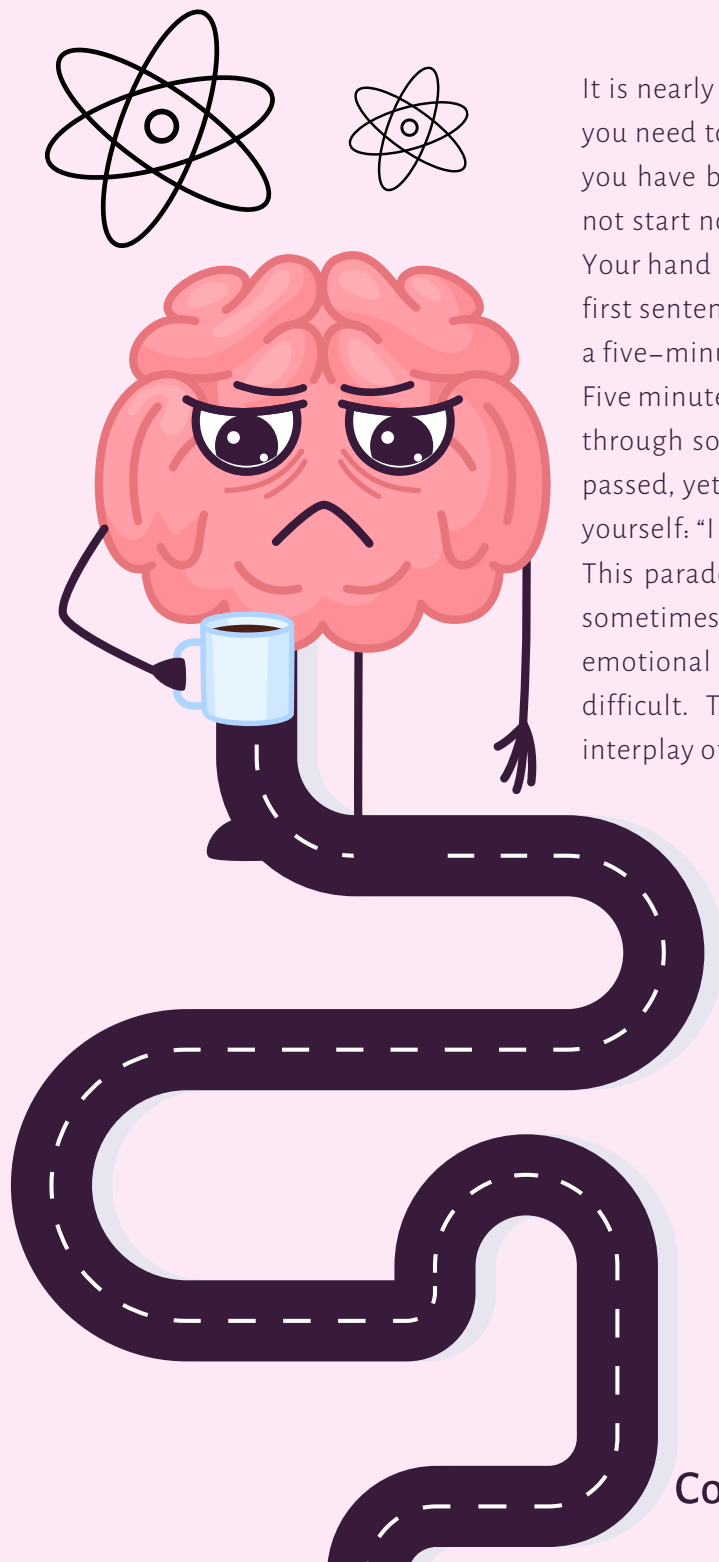
It is my earnest hope that our pursuit of progress remains deeply rooted in reality, truth, integrity, and righteousness. I sincerely hope that we learn to place greater value on the young generation we have today and the noble profession to which we have dedicated our lives.

We must strive to cultivate individuals capable of transforming unfavorable conditions into desirable, meaningful outcomes. While this is an attainable goal, it is a process that requires patience, as it unfolds gradually over time. Furthermore, we must learn to master the art of leveraging technological advancements and social media for constructive growth, while remaining vigilant against their detrimental effects and the peril of losing ourselves in empty distractions."



The “Later” Trap: The Anatomy of a Biological Escape

A Neurophysiological Perspective on Procrastination: The Hidden Battle Within Decision-Making Circuits



It is nearly 11 p.m. Your laptop screen is glowing, and the paper you need to submit tomorrow is still on its first page. For hours, you have been meaning to start. You even know that if you do not start now, you will be under even more pressure tomorrow. Your hand moves toward the mouse, but before you can type the first sentence, a simple thought crosses your mind: “I’ll just take a five-minute break, then I’ll start.”

Five minutes turn into half an hour—a short video, a quick scroll through social media—and suddenly you realize that time has passed, yet the task remains untouched. For a moment, you ask yourself: “I knew this was important, so why didn’t I do it?”

This paradox lies at the core of procrastination: the brain may sometimes choose immediate relief from an unpleasant emotional state, even when that choice makes the future more difficult. The question is: what happens within the hidden interplay of brain networks during this struggle?

Procrastination: A Problem of Emotion, Not Time

Contrary to popular belief, procrastination is not synonymous with laziness. Nor is it simply a lack of motivation or interest. In procrastination, individuals postpone a task despite recognizing its importance and the negative consequences of delay—and may even experience distress because of that postponement [1].

Contemporary research conceptualizes procrastination as a form of self-regulation failure: a difficulty in aligning present behavior with a goal that is valuable for the future [1].

A demanding task is not merely a sequence of logical steps. It may also evoke fear of failure, uncertainty, or perfectionistic concerns. Under these conditions, the brain must weigh the value of a future reward against the immediate affective cost of engaging in the task [1, 2].

If initiating the task evokes anxiety, avoiding it can produce an immediate reduction in psychological distress. This process is known as negative reinforcement: a behavior becomes more likely to recur because it reduces or removes an aversive state, such as anxiety, fear, or psychological distress.

The Battle Between Neural Circuits: Immediate Reward vs. the Distant Future

One important contributor to procrastination is the way the brain evaluates outcomes across time. Immediate rewards are generally weighted more heavily than delayed rewards—a phenomenon known as temporal discounting, in which the subjective value of an outcome decreases as the delay to that outcome increases [1, 3].

This helps explain why the statement “I’ll start tomorrow” can seem entirely reasonable in the moment.

The mind postpones the demanding task to a future point at which it imagines having more energy and experiencing less stress [2].

Three major neurocognitive systems are particularly relevant to this conflict:

1. Executive control network (ECN), particularly the prefrontal cortex:
2. This system helps keep goal representations active and resist distraction from competing stimuli [4, 5].
3. Emotion- and salience-processing systems, including the amygdala and insula:
4. In individuals prone to procrastination, task initiation may be processed as emotionally threatening. Neuroimaging studies suggest that functional connectivity between prefrontal regions and the insula is associated with emotion-regulation capacity and lower levels of procrastination [4].
5. Reward and dopaminergic systems:
6. Dopamine is not simply a “pleasure chemical.” Dopaminergic signaling contributes to reward learning, motivation, and behavioral value updating. When task avoidance produces temporary relief, that relief can function as a reinforcing outcome, increasing the likelihood that avoidance will be repeated in the future (Figure 1) [1, 2].



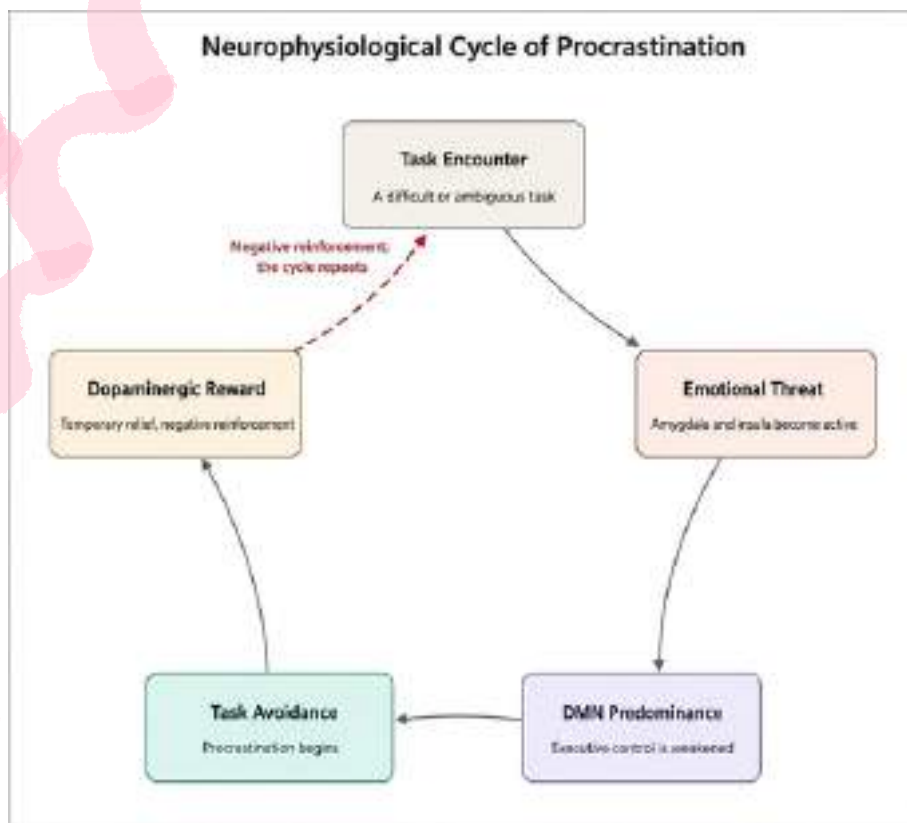


Figure 1. The Self-Reinforcing Cycle of Procrastination Encountering a demanding task may be processed by the amygdala and insula as an emotional threat. The relative predominance of internally oriented processing within the default mode network (DMN), together with reduced prefrontal executive control, may facilitate task avoidance. The temporary relief produced by avoidance functions as a reinforcing outcome, increasing the probability that the same avoidance response will recur during future encounters with the task—a process consistent with negative reinforcement.

From “Thinking” to “Doing”

The Prison of Thought: When the Brain Remains Stuck in the “Thinking” Stage

Sometimes the problem is not that we are unaware of the consequences of postponing a task. Rather, the difficulty lies in the transition from intention to action.

This is where the default mode network (DMN) becomes relevant. The DMN is naturally more active when attention is directed inward—for example, during mind-wandering, daydreaming, self-referential thought, or the mental review of personal concerns.

In individuals prone to procrastination, coordination between large-scale brain networks may become less efficient. fMRI studies suggest that executive networks involved in goal-directed control may be less effective at regulating internally oriented processing associated with the DMN. As a result, the individual may remain engaged in repetitive thoughts, imagined scenarios, and internal analyses surrounding the task, without successfully moving from the world of thought into goal-directed action. (Figure 2).

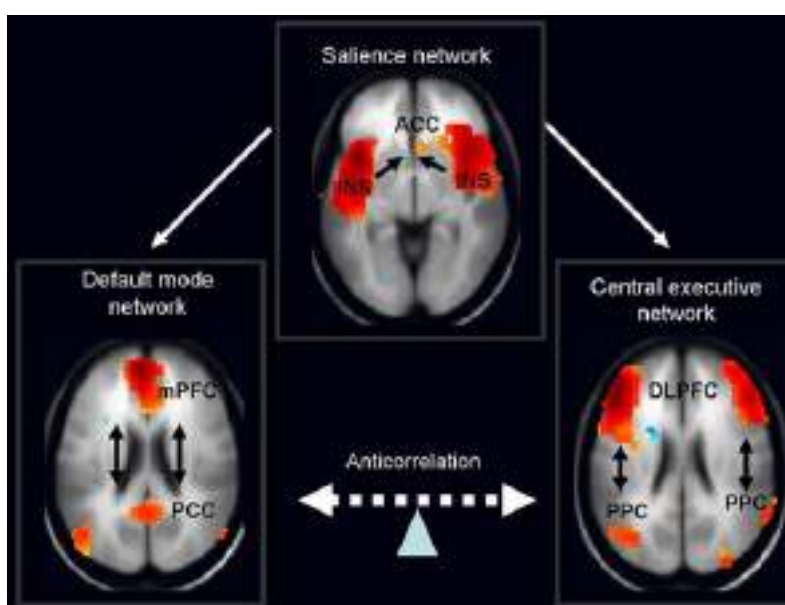


Figure 2. Dynamic interaction among the default mode network (DMN), salience network (SN), and executive control network (ECN) underlying the shift from internally oriented processing to goal-directed behavior.



Difficulty switching between internally oriented thought and goal-directed behavior may become particularly pronounced in certain clinical conditions and psychological traits:

- In ADHD: impaired attentional and executive control may make it more difficult to maintain goal-directed behavior in the presence of competing stimuli, causing attention to repeatedly drift away from the intended task.
- In perfectionism: internally generated thoughts may become dominated by self-criticism and fear of an imperfect outcome. Task initiation can therefore be appraised as highly threatening, leaving the individual trapped in hesitation rather than action [1, 2].

Which Procrastination Pattern Do You Most Often Show?

A practical framework discussed by Neuroscience News in relation to Itamar Shatz's book *Solving Procrastination* describes nine procrastination patterns [6]. Each pattern reflects a different psychological trigger that may become active before a task is postponed. Three commonly recognizable examples are described below.

A perfectionistic procrastinator may stare at the same paragraph for hours, delete it, rewrite it, and delete it again—not because they do not know what to write, but because no version seems “good enough.” The brain evaluates beginning the task not as a simple first step, but almost as a final examination of competence.

A worried procrastinator may mentally rehearse numerous failure scenarios before writing even a single sentence. “What if it gets rejected?” becomes so dominant that the individual postpones action because of catastrophic thinking.

A zigzag procrastinator sits down at the desk, opens a browser tab to check “just one source,” and half an hour later is reading something entirely unrelated. Each new stimulus pulls attention away from the primary task.

The remaining six patterns follow a similar logic but involve different triggers. The Pessimist anticipates that the outcome will be pointless before even beginning. The Dreamer becomes so absorbed in imagining the outcome that the first concrete step is never taken. The Rebel experiences the task as externally imposed and resists it.



A Brief Exercise: Which Pattern Feels Most Familiar?

Pattern	Statement Closest to Your Experience
Worrier	“What if the outcome is bad?” So, for now, I do not start.
Pessimist	“There is no point.” So I postpone the effort.
Perfectionist	“I’m not ready to do it perfectly yet.”
Dreamer	I think about the task a great deal, but I do not take the first step.
Zigzagger	Every new message or stimulus pulls me away from the main task.
Rebel	Because the task feels imposed on me, I resist doing it.
Thrill-seeker	Only the pressure of an approaching deadline gets me moving.
Hedonist	I choose the easier and more enjoyable option available right now.
Burnout	Almost every task feels as though it requires too much energy.



The Thrill-seeker becomes motivated only when the deadline is imminent. The Hedonist chooses the easier and more immediately rewarding option over sustained long-term effort. Finally, the Burnout procrastinator experiences even relatively simple tasks as requiring more energy than is readily available.

These nine patterns are not clinical diagnoses or neurophysiological classifications. Rather, they provide a simple framework for identifying the trigger that tends to become active immediately before procrastination occurs. The rule of this exercise is simple: choose only one or two statements that resemble your experience most closely, and then ask yourself:

“What am I trying to escape from in this moment—fear, uncertainty, boredom, or exhaustion?”

The answer is not a clinical diagnosis. It is simply a clue that may help identify where the first effective step toward action should begin.

A behavior that appears identical on the surface may arise from very different triggers: fear and catastrophizing in the Worrier, expectations of failure in the Pessimist, fear of an imperfect outcome in the Perfectionist, attentional shifting and distractibility in the Zigzagger, or a preference for immediate reward in the Hedonist.

This interpretation is broadly consistent with research implicating task aversiveness, emotion regulation, impulsivity, and temporal discounting in procrastination. However, these labels themselves should not be interpreted as established clinical categories [1, 2].

From this perspective, the solution is unlikely to be identical for everyone. For the Perfectionist, defining an “acceptable version” rather than a “perfect version” may be particularly important. For the Zigzagger, reducing competing stimuli and translating vague goals into concrete steps may be more useful. For the Worrier, identifying catastrophic predictions may be the critical first step. For the Burnout procrastinator, it is important to distinguish task avoidance from a genuine limitation caused by fatigue.

This framework is intended for self-reflection, not self-diagnosis [6].

Breaking the Cycle: Building Your Future Brain

One crucial principle is that the brain is not static. Through neuroplasticity, experience can modify patterns of neural activity and connectivity. Just as repeated avoidance can establish familiar behavioral patterns, new experiences can support alternative patterns of responding.

Reducing the size of the first step—for example, “I’ll work on it for only five minutes”—may alter threat-related predictions associated with task initiation. Once the task has begun, the anticipated cost of performing it may decrease as direct experience replaces the anxiety-provoking representation imagined beforehand [2, 3].

Procrastination is not the story of a lazy brain. It is the story of a brain caught between two competing worlds: immediate reward and long-term goals.

Each time we take even a small step despite discomfort, we begin to shift the balance of that competition. We are not merely products of our brain activity; our experiences also shape the brain itself.

Perhaps this is one of the most important lessons of neuroscience: our brains have been shaped by our past, but with every new choice, we participate in reshaping neural connections and building the brain of our future.

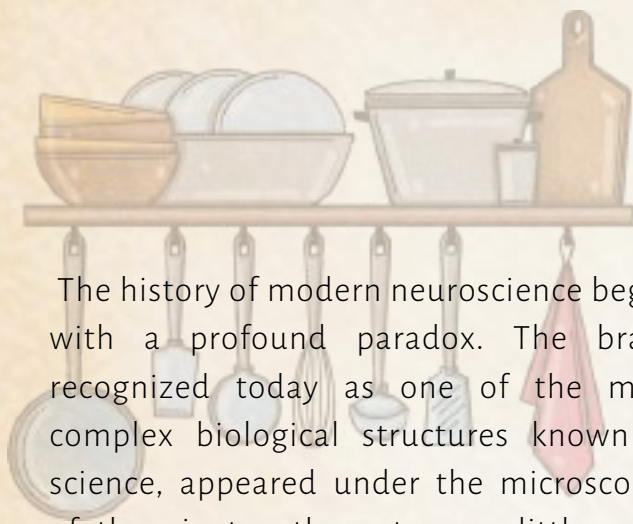
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ALCHEMY IN A HOSPITAL KITCHEN: THE GENEALOGY OF HISTOLOGICAL STAINING AND THE BIRTH OF MODERN NEUROSCIENCE

Compiled by: Amin Vahabzadeh



The history of modern neuroscience began with a profound paradox. The brain, recognized today as one of the most complex biological structures known to science, appeared under the microscopes of the nineteenth century as little more than a homogeneous, gelatinous mass devoid of clearly distinguishable boundaries. Today, it is self-evident that the cerebral cortex is composed of billions of neurons interconnected through an immense network of processes. However, until the 1870s, the limited resolution of techniques available for visualizing the fine architecture of neural tissue prevented scientists from appreciating its precise structural organization [1].

By that time, fixation and staining techniques in general anatomy had undergone considerable development. Scientists could readily distinguish hepatic cells and muscle fibers using natural dyes such as carmine and hematoxylin. Neuroanatomy, however, remained at a major impasse.

The brain presented two particularly challenging characteristics that rendered the histological tools of the era largely ineffective:

1. The extraordinarily high density and extensive intermingling of cellular processes, collectively forming the neuropil.
2. Its high lipid content, particularly the sphingolipids and cholesterol-rich membranes of myelin.

The commonly used dyes of the time either failed to penetrate neural tissue effectively because of its hydrophobic nature or

stained virtually all cellular structures simultaneously and uniformly. The resulting microscopic image was therefore obscure and poorly resolved—much like a dense rainforest in which the boundaries of an individual tree cannot be distinguished from those of neighboring trees because of the overwhelming density of foliage. Prominent anatomists such as Johannes Purkinje and Otto Deiters attempted to overcome this problem by producing extremely thin sections with very sharp blades, thereby physically reducing tissue density; nevertheless, cellular boundaries remained indistinct [1].

When Neurons Were Seen for the First Time

In 1873, this historical impasse was broken by Camillo Golgi, a young physician who, owing to financial constraints, had been forced to abandon his academic position and accept the superintendence of a hospital for chronically ill patients in the small town of Abbiategrasso. He established a rudimentary laboratory in the kitchen of his residence, where he developed a new protocol that would later become known as the Golgi stain or Golgi impregnation method [2].

In this technique, Golgi initially fixed brain tissue in a solution of potassium dichromate. This biochemical step not only increased tissue rigidity but also prepared the tissue for the subsequent penetration of ions into cellular structures. The fixed tissue was then transferred into a solution of silver nitrate. At this stage, silver ions reacted with the chromate ions that had penetrated the tissue, resulting in the formation of silver chromate crystals. These dark brown or black precipitates accumulated within the neuronal soma and cellular processes [2].

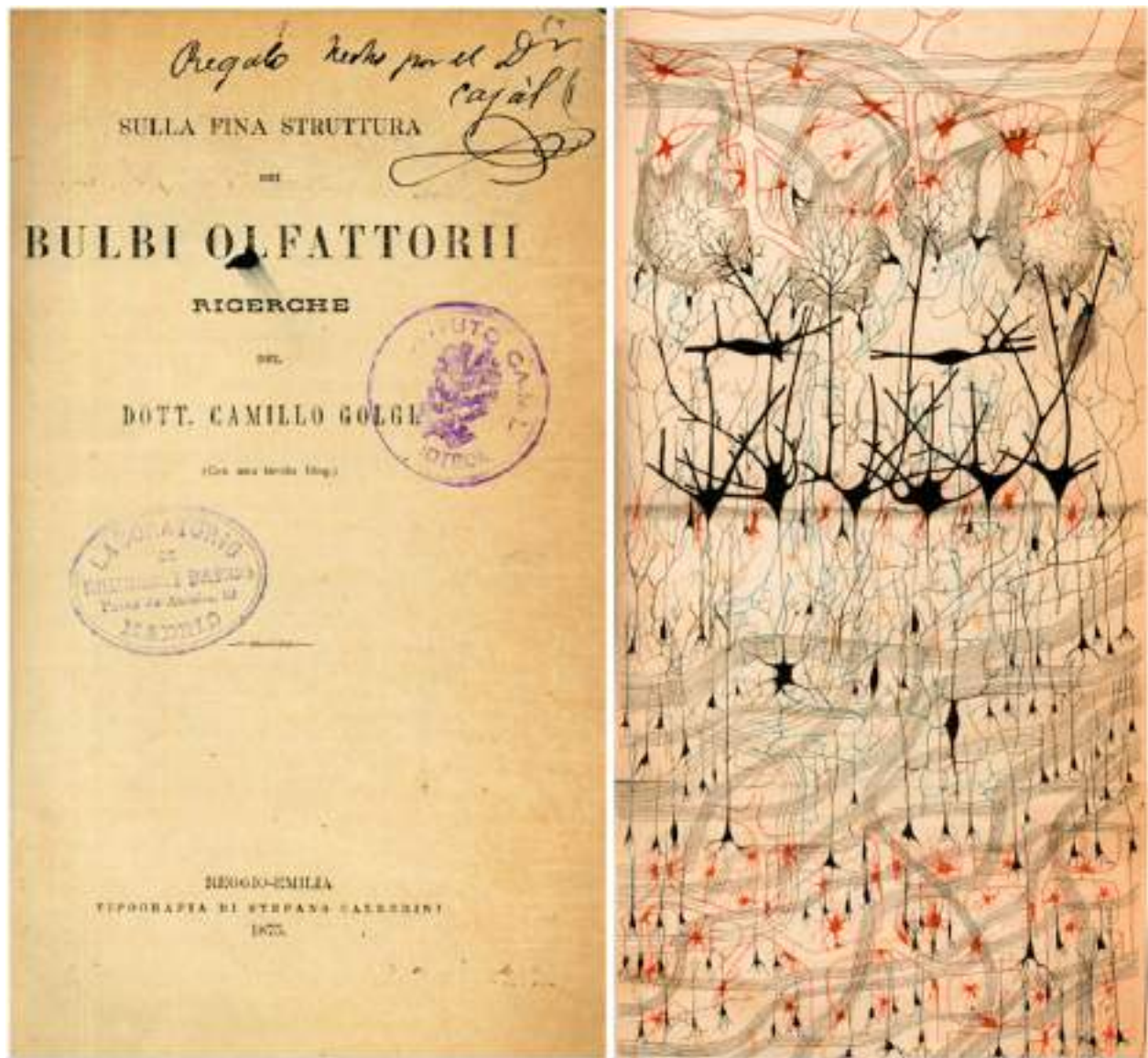


Figure 1. The Golgi method and the first detailed visualization of neuronal architecture.

The first illustration of a Golgi-impregnated preparation of the nervous system, depicting a vertical section of the olfactory bulb of a dog. By selectively impregnating a small proportion of neurons while leaving most surrounding cells unstained, the Golgi method transformed the apparently impenetrable neural tissue into a preparation in which individual neuronal cell bodies and processes could be followed in considerable detail. This selective contrast provided one of the essential visual foundations for the emergence of modern neuroanatomy.

DeFelipe J. Cajal and the discovery of the Golgi method: a neuroanatomist's dream.
 Anat Sci Int. 2025;100(4):384–399. doi:10.1007/s12565-025-00840-7.

The Clash of Two Perspectives and the Ascent to the Peak of the World's Greatest Scientific Honor

This powerful morphological tool reached Santiago Ramón y Cajal, the patient Spanish anatomist, in 1887. Cajal recognized several limitations of Golgi's original method: silver deposits could sometimes be unstable, while the extensive presence of myelin in mature neural tissue interfered with the precise tracing of axonal trajectories [3].

Cajal introduced two strategic modifications to the protocol:

First, double impregnation: he repeated the fixation and silver-impregnation process, increasing the density of the deposits and revealing delicate structures such as dendritic spines.

Second, adoption of an ontogenetic approach (examining the brain during early developmental stages): rather than focusing primarily on the adult brain, which possesses a more complex neural network and abundant myelination, Cajal examined embryonic brains and those of newborn animals. At these developmental stages, the neural network is less densely packed and myelination has not yet become extensive. This relative structural simplicity allowed him to trace the trajectory of individual nerve fibers (axons) with unprecedented clarity [3].

This technical optimization provided the spark for one of the greatest intellectual confrontations in the history of science. Based on his observations of Golgi-stained preparations, Camillo Golgi adhered to the reticular theory, arguing that the nervous system constituted a continuous cytoplasmic network, or syncytium, analogous in some respects to the vascular system [2]. In contrast, drawing on his improved preparations, Cajal observed the physical individuality of individual cells and demonstrated that neurons are discrete structural and functional

units that communicate through specialized contacts across microscopic gaps—the synaptic clefts. This concept, which became known as the neuron doctrine, brought the principles of cellular biology into the study of the brain.

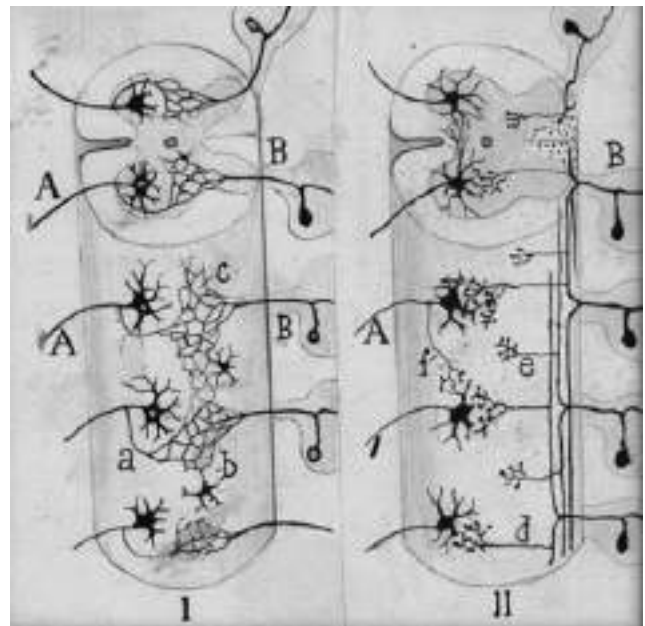


Figure 2. From the reticular theory to the neuron doctrine. Cajal's schematic comparison of the reticular theory (I) and the neuron doctrine (II), illustrating two fundamentally different interpretations of nervous-system organization. Whereas the reticular view conceived neural processes as components of a continuous network, Cajal's interpretation emphasized the individuality and discrete organization of nerve cells. The figure represents the conceptual conflict that transformed the Golgi method from a technique for visualizing neural morphology into a tool for testing competing theories of brain organization.

The disagreement was so profound that even when the two scientists jointly received the 1906 Nobel Prize in Physiology or Medicine, Golgi used his Nobel lecture to characterize the neuron doctrine as an outdated hypothesis. The following day, Cajal defended his hypothesis by presenting compelling anatomical evidence in support of neuronal individuality [4].

The Legacy of the Industrial Revolution in Mapping the Cerebral Cortex: How Specialized Stains Emerged

Despite the effectiveness of the Golgi method for examining the morphology of individual neurons, its sparse and selective staining pattern prevented it from revealing the overall organization and laminar architecture of the brain. By the late nineteenth century, Germany had established dominance over the emerging industry of synthetic organic dyes, particularly aniline dyes derived from coal tar. This industrial capacity helped transform German universities into leading centers of histological research.

During this period, Franz Nissl discovered that basophilic dyes such as cresyl violet exhibited a strong electrostatic affinity for acidic intracellular components, particularly nucleic acids and, most notably, ribosomal RNA. In

neurons, the structures that became known as Nissl bodies corresponded primarily to the densely packed rough endoplasmic reticulum within the soma and proximal dendrites. Because axons lack rough endoplasmic reticulum, they remained unstained by the Nissl method. This distinction enabled Korbinian Brodmann, through systematic examination of the cellular architecture of the cerebral cortex, to construct his famous map of 52 cortical areas [1]. At approximately the same time, Carl Weigert developed a staining method using hematoxylin modified with copper salts that preferentially targeted the lipids of the myelin sheath. In contrast to Nissl staining, this technique highlighted the brain's communication cables—the white matter—by darkening myelinated fiber tracts and thereby revealing the brain's major pathways of connectivity [1].

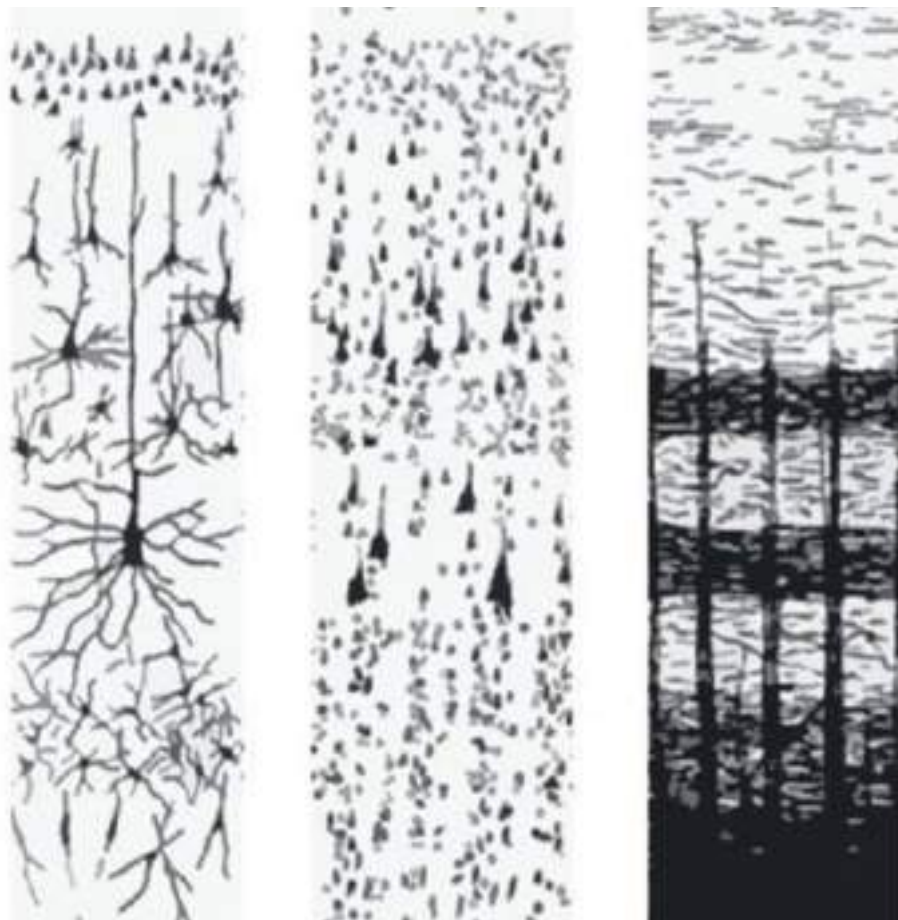


Figure 3. Seeing the cortex through different stains: Golgi, Nissl, and Weigert. Nineteenth-century histological views of the cerebral cortex obtained through complementary staining strategies. The Golgi method emphasizes the morphology of individual neurons and their processes; Nissl staining reveals the distribution and organization of neuronal cell bodies; and Weigert staining highlights myelinated axonal projections and fiber architecture. Together, these approaches illustrate a crucial transition in neuroanatomy—from identifying individual cellular elements to describing the layered and interconnected architecture of the brain.

REREADING THE BRAIN'S IDENTITY WITH FLUORESCENT NEURONS

By the second half of the twentieth century, classical histology had encountered a major limitation: these staining methods could not provide functional or molecular specificity. To conventional histological stains, a dopaminergic neuron was essentially indistinguishable from a serotonergic neuron. To overcome this limitation, scientists developed immunohistochemistry. Fluorescently labeled antibodies were employed as highly specific molecular probes capable of binding to proteins characteristic of particular cell types, thereby enabling chemical and molecular mapping of the brain [6].

But the next major question was this: What if the neuron itself could emit light without requiring an externally applied dye?

The answer was hidden in the genome of a hydrozoan jellyfish that naturally produces green fluorescent protein (GFP). In a revolution in genetic engineering, scientists transferred

the genetic sequence encoding this protein into the genomes of laboratory animals, enabling neurons within a living brain to produce fluorescent proteins themselves [7].

However, in the densely packed environment of the brain, when millions of neurons all emitted the same green fluorescence, distinguishing individual neuronal processes remained difficult. In 2007, researchers at Harvard University addressed this problem by introducing the technique known as Brainbow. Using stochastic genetic recombination, they expressed genes encoding multiple fluorescent proteins in the genomes of mice. Random combinations of these fluorescent proteins within individual cells—analogueous to the mixing of colored pixels in a display—caused each neuron to acquire a distinctive and essentially unique color signature. The technique was therefore analogous to color-coding the wiring of a supercomputer, allowing

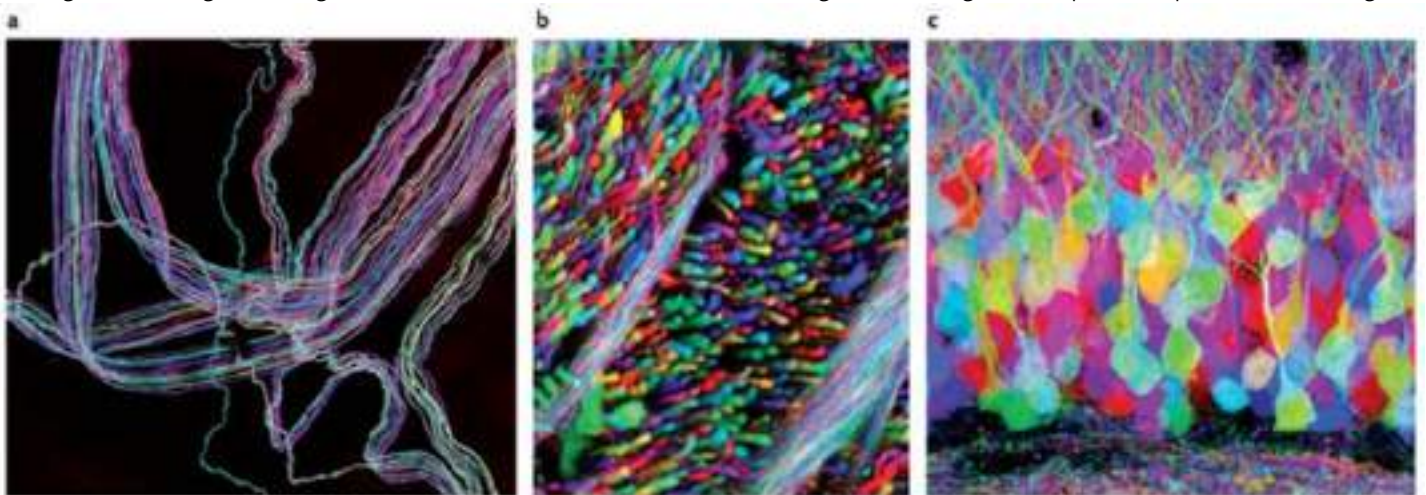


Figure 4. Brainbow: assigning colour to the neural wiring.

Multicolour neuronal labeling in Brainbow transgenic mice. Different combinations of fluorescent proteins generate distinct colour signatures in neighboring neurons, allowing individual axons and neuronal processes to be distinguished within densely packed neural tissue. In this way, the problem that confronted classical histology—how to follow one neuronal process through a crowded network—was approached by replacing selective chemical staining with genetically encoded combinatorial fluorescence. Panels show multicolour labeling in a motor nerve, an axon tract in the brainstem, and the hippocampal dentate gyrus.

researchers to trace individual “wires,” or neuronal processes, through thousands of neighboring fibers. It became possible to follow a purple neuronal process through a dense forest of neighboring cyan and orange branches [8].

Journey into the Glass Brain: CLARITY and Three-Dimensional Resolution

The final major obstacle was the intrinsic opacity of the brain, largely attributable to its high lipid content, particularly myelin, which interferes with the transmission of light through tissue. For many years, the only practical way to visualize structures deep within neural tissue was to mechanically section the brain, a process that inevitably disrupted long-range anatomical connections. In 2013, the remarkable CLARITY technique overcame this limitation. In this approach, brain tissue is first embedded within a polymerized hydrogel matrix that forms a physical scaffold for preserving proteins and nucleic acids. Subsequently, light-scattering lipids are removed from the tissue using detergents, facilitated by an applied electrical field. The result is a highly transparent, glass-like brain in which the three-dimensional architecture of neuronal structures can be preserved while permitting deep-tissue imaging [5].

Almost simultaneously, an inverse strategy known as expansion microscopy was introduced. Rather than attempting to force light through densely packed tissue, this approach embeds the specimen within a highly water-absorbing hydrogel and induces uniform physical

expansion in all directions. This expansion increases the physical distance between target molecules, enabling structures that were previously below the diffraction-limited resolution of conventional light microscopy—approximately 200 nm—to be visualized with substantially greater spatial resolution [9].

The Brain's Fabric Through Time: From Classical Histological Staining to Digital Connectomics

Today, large-scale connectomics projects are attempting to reconstruct comprehensive maps of the brain's synaptic connectivity. For example, the international FlyWire consortium has successfully reconstructed the complete neuronal connectivity of the adult fruit-fly brain, while the MICrONS project has reconstructed an entire cubic millimeter of mouse cerebral cortex at synaptic resolution. These achievements were recognized by the prestigious journal *Nature Methods* as the method of the year in neuroscience [10].

Despite relying on sophisticated machine-learning algorithms and advanced electron microscopy, these projects remain grounded in the same conceptual principle that Cajal established with a paintbrush and a relatively simple microscope: creating contrast within densely packed biological structures in order to make the invisible visible.

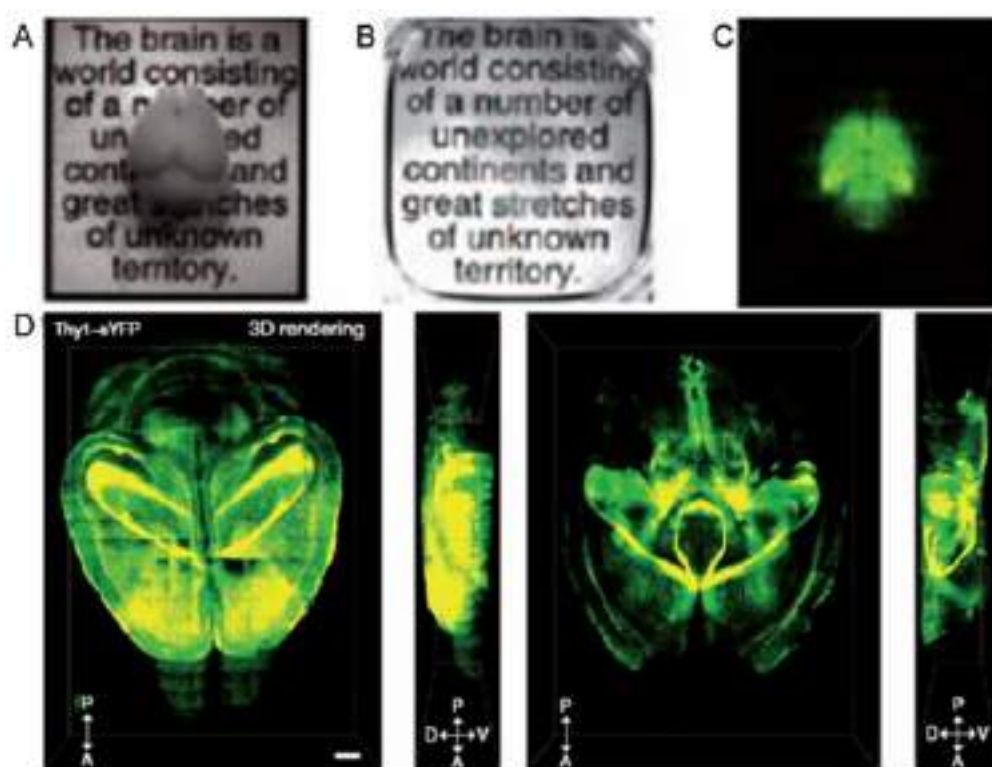


Figure 5. CLARITY: transforming the opaque brain into a three-dimensional imaging substrate.

The principle and visual outcome of CLARITY-based tissue clearing. An intact mouse brain is shown before and after lipid removal, followed by fluorescence imaging and three-dimensional reconstruction. By combining a hydrogel-based tissue scaffold with lipid extraction, CLARITY reduces the optical opacity of brain tissue while preserving anatomical and molecular information, allowing neuronal structures to be examined throughout intact tissue rather than only in mechanically sectioned slices.

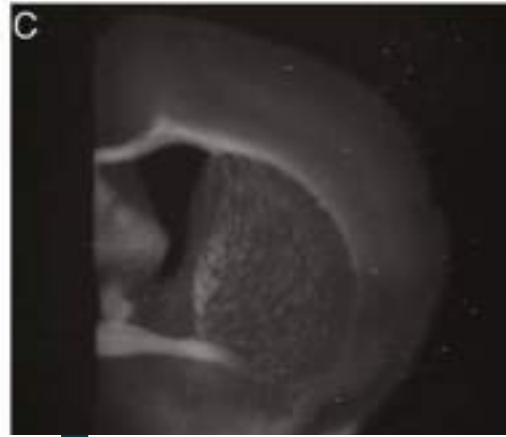


Figure 6. Expansion microscopy: increasing physical scale to reveal the microscopic.

Overview of expansion microscopy and its effect on tissue dimensions. A biological specimen is chemically fixed and embedded within a swellable hydrogel, which is subsequently expanded in water. The resulting physical enlargement increases the spatial separation between molecular structures, allowing features that are difficult to resolve by conventional light microscopy to be visualized at higher effective resolution. Panels A–C illustrate the basic process and the corresponding expansion of a fixed mouse brain specimen.

It is a story that began in the darkness of a small kitchen in Italy and has now culminated in the digital, three-dimensional mapping of the connectivity underlying the mind. Today, with microscopes costing millions of dollars, we continue to ask essentially the same question that Golgi confronted in his modest kitchen laboratory: How does this structure give rise to consciousness?

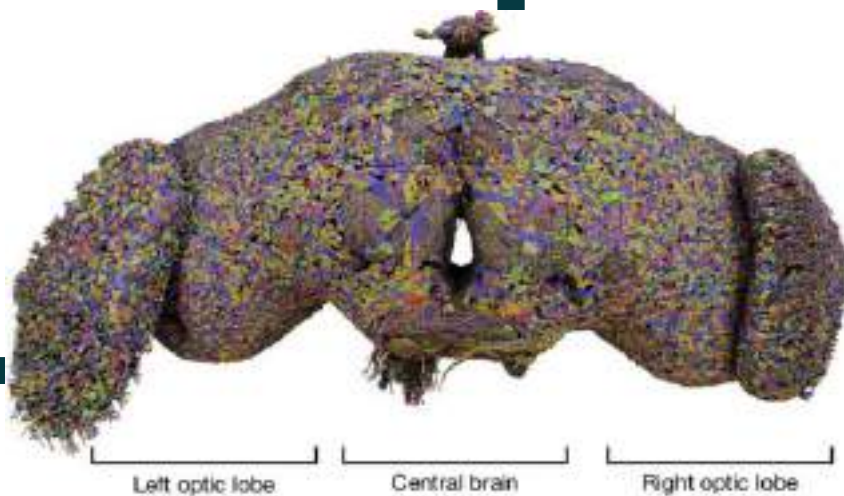


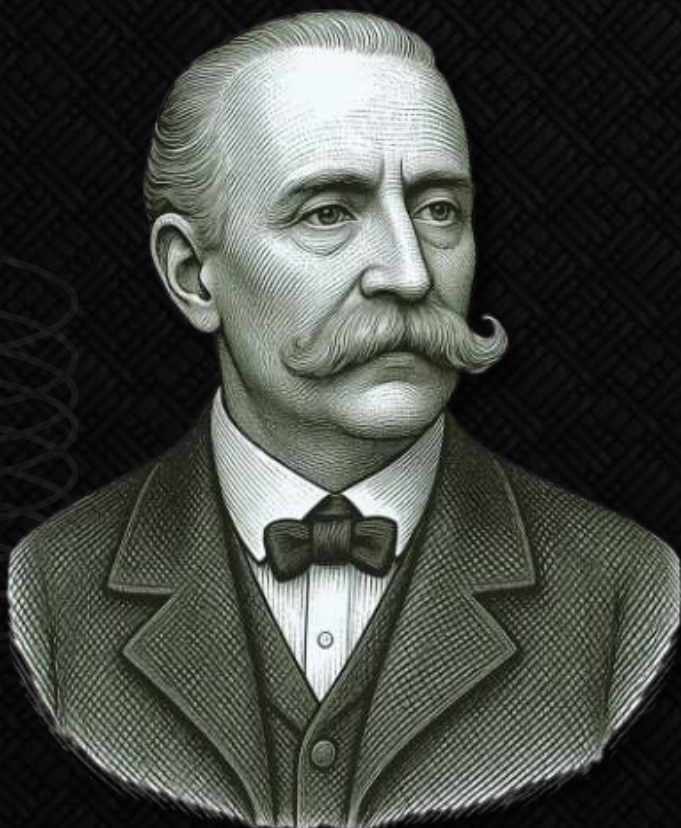
Figure 7. FlyWire: from neuronal morphology to a whole-brain connectome.

Three-dimensional reconstruction of the neuronal architecture of an adult fruit fly brain using the FlyWire connectomic platform. Individual neuronal morphologies were digitally segmented and proofread across the central brain and optic lobes, transforming microscopic anatomical information into a navigable representation of whole-brain wiring. This image illustrates the culmination of the historical trajectory described in this article: from Golgi's selective visualization of individual neurons to the computational reconstruction of neuronal networks at whole-brain scale.

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THE BLACK REACTION: WHEN AN UNEXPECTED STAIN REVEALED THE SECRETS OF NEURONS

In 1872, in the small kitchen of a young physician's residence at the Abbiategrasso Psychiatric Hospital near Milan, experiments were being conducted that few could have imagined would permanently change the course of neuroscience. Camillo Golgi, who lacked access to a well-equipped laboratory, developed a technique using several chemical solutions, considerable patience, and months of trial and error. This method later became known as the "Black Reaction." For the first time, this technique made it possible to visualize an entire neuron, from its cell body to its finest dendritic and axonal branches. This achievement not only revolutionized the study of the brain structure but also altered the course of one of the greatest controversies in the history of neuroscience.



Why Was It Difficult to Visualize Neurons?

During the second half of the nineteenth century, the study of the central nervous system faced a fundamental obstacle. The extremely high density of neurons and the intricate intermingling of axons and dendrites meant that, despite advances in light microscopy, brain tissue appeared under the microscope as a dense mass without clearly distinguishable cellular boundaries.

Conventional histological staining methods, such as carmine and hematoxylin, although effective for visualizing many tissues of the body, often stained large numbers of cells at the same time in nervous tissue. This made it difficult, if not impossible, to trace the course of an individual neuron.

This observational limitation left one of the most fundamental questions in neuroscience unanswered: Is the nervous system composed of independent cells, or does it form a continuous network of interconnected cellular structures?

At that time, the reticular theory, supported by scientists such as Joseph von Gerlach, proposed that neuronal processes were connected at various points throughout the brain, forming an integrated neural network. In contrast, the view that later became known as the neuron doctrine emphasized the individuality of nerve cells and their communication through specialized connections.

How Did a Simple Staining Technique Revolutionize Neuroanatomy?

To address this problem, a method was needed that could reveal the complete structure of an individual neuron within a dense population of neural cells.

Camillo Golgi, a young Italian physician, began experiments to improve methods for staining nervous tissue in 1872, while working at the Abbiategrasso Psychiatric Hospital near Milan. Despite limited laboratory resources and after months of trial and error, he introduced a technique in 1873 that later became known as the Black Reaction.

This technique produced high contrast and selectively stained a limited number of neurons, allowing the complete morphology of an individual cell to be visualized. Unlike methods that resulted in widespread staining throughout the tissue, most cells remained unstained in the Black Reaction, while only a small number of neurons became clearly visible.

This feature allowed researchers to trace the entire course of a neuron, from its cell body to its dendritic and axonal branches.

This unique characteristic transformed the Black Reaction into one of the most important tools in the history of neuroanatomy and provided important structural evidence contributing to the development of the neuron doctrine. However, the ultimate interpretation of these observations supported the neuron doctrine, contrary to Golgi's own theoretical position [1].

Golgi, Cajal, and the Great Neuron Doctrine Controversy

At a time when the true structural organization of neurons remained unclear, the European scientific community was divided between two major views concerning the organization of the nervous system.

Supporters of the reticular theory believed that nerve cells were physically interconnected and formed a continuous neural network. In contrast, proponents of the neuron doctrine argued that the nervous system was composed of independent cellular units that interacted with one another through specialized connections.

Golgi's staining technique made it possible to directly visualize neuronal structures and became one of the most important tools for resolving this historical controversy. However, the final interpretation of these observations contradicted the theoretical position of the very scientist who had developed the technique.

Mechanism of the Black Reaction: How Was a Single Neuron Revealed?

The Golgi Black Reaction is based on the formation of dark-colored silver chromate precipitates within certain nerve cells.

In this method, nervous tissue is first exposed to chromate compounds and is subsequently treated with silver salts. Silver chromate crystals then form within certain regions of the neurons. The accumulation of these precipitates within the cells causes the cell body, dendrites, and axon to become visible with high contrast against a relatively clear background.

The most remarkable feature of this technique is its selective staining. Only a small proportion of neurons—approximately 1–5%—become stained, while most surrounding cells remain unstained. Although this characteristic may initially appear to be a limitation, it is actually the principal advantage of the Black Reaction. It allows researchers to trace the entire morphology of an individual neuron without interference from the dense population of neighboring cells.

Although more than a century has passed, the precise mechanism underlying this selective staining has not been completely elucidated. Differences in cellular chemistry, intracellular characteristics, and tissue microenvironment are thought to contribute to the formation of these precipitates.

The outcome is a clear representation of the architecture of an individual neuron—a visualization that, for the first time, enabled more detailed investigation of the spatial organization of neural cells and facilitated the development of hypotheses concerning the relationship between neuronal structure and function.

For this reason, the Black Reaction is not merely a staining method; it represents a landmark in the history of neuroanatomy. The technique paved the way for a deeper understanding of the cellular organization of the brain, the investigation of neural connectivity, and the development of new concepts concerning nervous system function [2].

By revealing neuronal processes within tissue sections, the technique allows researchers to examine and partially reconstruct the three-dimensional morphology of neurons. In contrast to many conventional staining methods, in which fine neuronal processes may be obscured by the large number of stained cells, Golgi staining facilitates the examination of a relatively isolated neuron against a clear background.

Consequently, the technique has become a valuable tool for investigating neuronal morphology, dendritic architecture, and morphological changes associated with experience, learning, and neurological disorders. Despite its apparent simplicity, the Black Reaction is a sensitive and somewhat unpredictable technique. Small differences in sample preparation and tissue characteristics can affect the final quality of staining.

This sensitivity, together with the selective nature of the precipitation process, is one of the reasons

Method	Year	Reagents	Structural/Biochemical	Main Application
Classical Golgi (Black Reaction)	1873	Potassium dichromate /	High contrast; complete	Historical studies and early
Golgi-Cox	1891	Mercuric chloride / potassium	High reproducibility	Gold-standard method for
Rapid Golgi	1933	Osmic acid / silver nitrate	Shorter processing time;	Investigation of immature and
Colonnier Golgi	1964	Glutaraldehyde / formaldehyde	Excellent preservation of	Studies combined with electron

Implementation of the Golgi Technique and Factors Affecting Staining Quality

Successful implementation of the Black Reaction differs fundamentally from many histological staining methods that aim to label large numbers of cells. Instead, it is based on generating high contrast in a limited population of neurons.

In this method, after preparation of nervous tissue with chromate compounds and exposure to silver salts, silver chromate precipitates form within selected neurons. This makes it possible to visualize the complete large numbers of cells large numbers of cells at the same time of these cells, from their cell bodies to their fine dendritic and axonal branches.

why the technique has retained a special position in neuroanatomical and neuroscience research for more than 150 years.

Comparative Analysis of Modified Golgi Staining Methods

Given the limitations of the classical Golgi method, modified approaches were developed beginning in the late nineteenth century to improve the reproducibility and practical applicability of the technique.



Methods such as Golgi–Cox, Rapid Golgi, and EM–Golgi introduced modifications in chemical composition and/or sample preparation, allowing more detailed investigation of neuronal morphology and its relationship to brain function [3].

Cajal’s Contributions to Neuroanatomy and the 1906 Nobel Controversy

Although the invention of the Black Reaction by Camillo Golgi represented a revolutionary advance in histology, the biological interpretation of this visual phenomenon gave rise to one of the most controversial and profound debates in the history of science. Influenced by the theoretical assumptions of the reticular theory and relying on images produced by his staining method, Golgi believed that neuronal axonal processes formed a structure known as the “diffuse neural network,” in which the cytoplasm of individual cells was physically continuous with that of other cells.

However, in 1887, the prominent Spanish anatomist Santiago Ramón y Cajal optimized Golgi’s method and applied it to embryonic and neonatal nervous tissue. Because myelination was not yet complete in these tissues, they provided greater structural clarity. Cajal made observations that were fundamentally inconsistent with Golgi’s interpretation. Through repeated staining procedures and detailed microscopic examinations, he concluded that each nerve cell was a completely independent cellular unit bounded by a distinct cell membrane. Although the processes of one neuron could come into close proximity to those of neighboring cells, they did not fuse with the cytoplasm of the neighboring cells. This interpretation provided strong support for the neuron doctrine. Cajal also introduced the concept of the law of dynamic polarization, which proposed that information in the nervous system generally follows a directional pathway: it is received through the dendrites, processed in the cell body, and transmitted through the axon toward the next cell.

This intense intellectual conflict reached its culmination in 1906, when the Nobel Prize in physiology or Medicine was jointly awarded to Golgi, in recognition of his development of the

staining technique, and Cajal, in recognition of his correct interpretation and demonstration of the cellular organization of the brain. The Nobel lectures of the two scientists became one of the most dramatic moments in the history of science. Golgi continued to defend the reticular theory and criticized Cajal’s findings, whereas Cajal, in his lecture the following day, presented detailed evidence and remarkable microscopic drawings emphasizing the structural independence of neurons and the existence of spaces between nerve cells, which were later understood as synaptic clefts [2,4].

From Dendritic Spines to Brain Disorders

One of the most remarkable and enduring structural discoveries made possible by Golgi staining was Cajal’s detailed description of dendritic spines. Before this discovery, dendrites were often regarded as relatively simple tubular structures or smooth tissue processes. However, the detailed images generated by the Black Reaction revealed that the surfaces of dendrites in many neurons—particularly pyramidal neurons of the cerebral cortex and Purkinje cells of the cerebellum—are covered with miniature, button-like protrusions that may have mushroom- or cone-like shapes. Initially, many of Cajal’s contemporaries regarded these small protrusions as laboratory artifacts or nonspecific silver precipitates resulting from imperfections in the staining protocol. However, Cajal demonstrated their biological stability by repeatedly observing the same structures in different specimens.

Today, more than a century later, modern imaging techniques, including electron microscopy and live fluorescence imaging, have established that dendritic spines are major sites of excitatory synapse formation in the mammalian brain.



Each dendritic spine functions as an independent biochemical microcompartment, containing a specific density of neurotransmitter receptors and contributing to the compartmentalization of postsynaptic calcium signalling. The significance of this discovery is particularly important in cognitive neuroscience. Structural changes in the number, volume, and morphology of dendritic spines—collectively referred to as structural plasticity—provide an important structural and functional basis for learning, memory, and the brain's adaptation to environmental conditions. The initial identification of these structures would have been extremely difficult, and perhaps impossible, without the high contrast provided by the Golgi method [5].

Why Has Golgi Staining Remained Relevant in the Twenty-First Century?

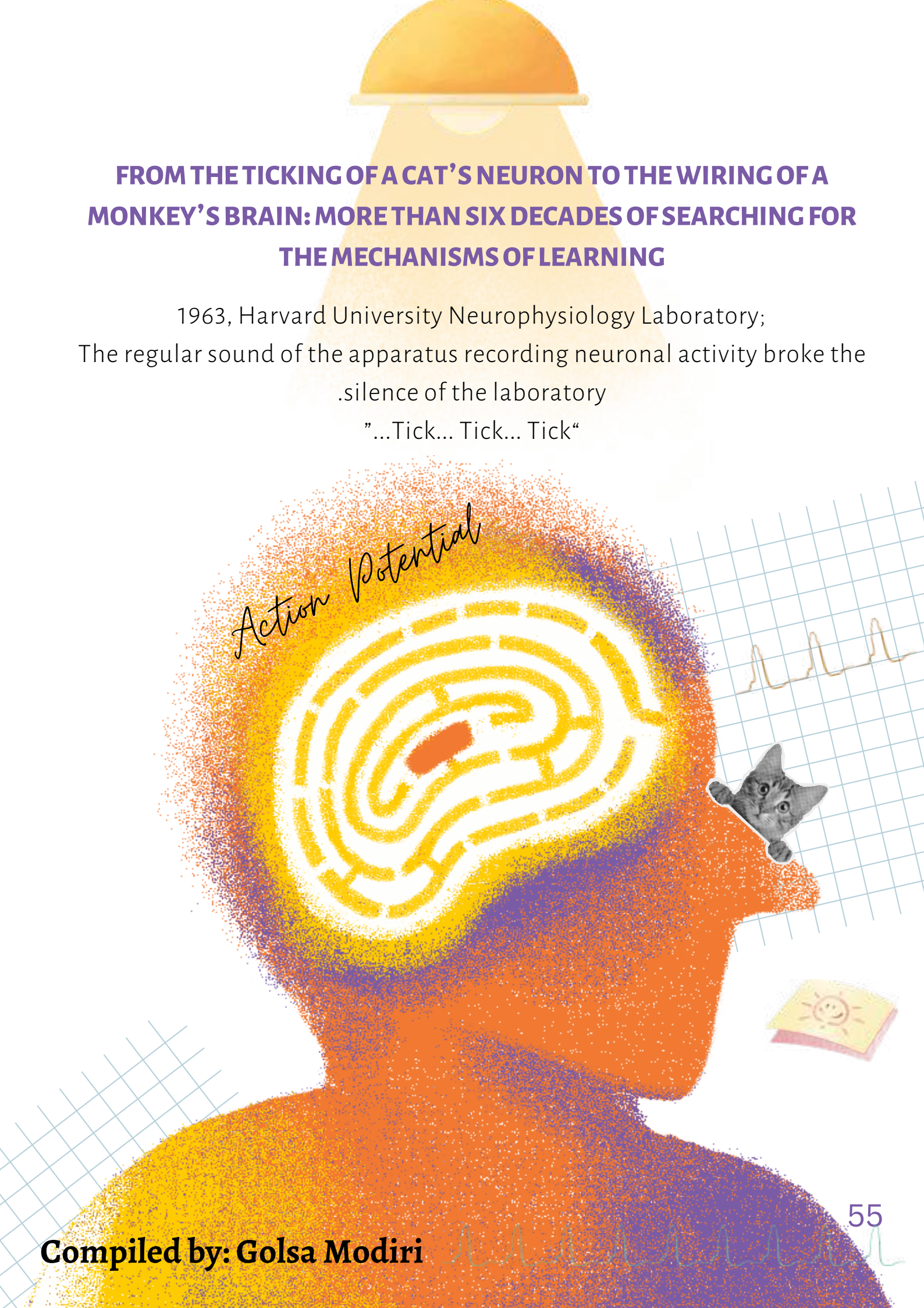
Despite the emergence of advanced imaging technologies such as two-photon microscopy and multicolor genetic labelling techniques such as Brainbow, Golgi staining continues to maintain an important position in neuroscience research. Its continued relevance can be attributed to its relative simplicity, low cost, and unique ability to reveal the complete morphology of an individual neuron, particularly its dendritic branches and dendritic spines. Modern methods allow simultaneous visualization of large numbers of neurons and investigation of complex neural connections. However, they often require sophisticated equipment, genetic manipulation, or specialized infrastructure. In contrast, modified Golgi methods such as Golgi-Cox remain accessible and valuable tools for investigating neuronal morphological changes in animal models. Today, this technique is used to study structural changes in the brain associated with learning, environmental experience, and neurological and psychiatric disorders. Changes in the number and morphology of dendritic spines, which are important indicators of synaptic plasticity, have been investigated in disorders including Alzheimer's disease, autism, schizophrenia, and certain neurodevelopmental disorders. Furthermore, combining Golgi staining with modern imaging techniques, three-dimensional reconstruction, and electron microscopy has made it possible to investigate the relationship between the fine structural features of neurons and the functional organization of neural networks. Thus, a technique that originated more than 150 years ago from an unexpected observation remains a valuable tool for understanding the complex architecture of the brain.

Final Remarks: The Story of Precise Observation

The Black Reaction was more than a staining technique; it provided a window into the hidden architecture of the brain. Golgi, through the development of an innovative method, and Cajal, through a more accurate interpretation of the findings obtained with that method, demonstrated that scientific progress does not always depend on increasingly complex tools. Sometimes, careful observation, the formulation of appropriate questions, and thoughtful interpretation can fundamentally change the course of an entire scientific field.

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FROM THE TICKING OF A CAT'S NEURON TO THE WIRING OF A MONKEY'S BRAIN: MORE THAN SIX DECADES OF SEARCHING FOR THE MECHANISMS OF LEARNING

1963, Harvard University Neurophysiology Laboratory;
The regular sound of the apparatus recording neuronal activity broke the
silence of the laboratory
"...Tick... Tick... Tick"

Action Potential

David Hubel and Torsten Wiesel had been recording the activity of cells in the visual cortex of a kitten for hours [1, 2]. A very fine electrode was positioned in the primary visual cortex (V1); the delicate electrode was used to record the activity of individual neuronal units. The cat's eyes were open, and lines with different orientations were displayed on a screen in front of it.

Each time a neuron became active, the loudspeaker produced a short sound.

"Tick... tick... tick..."

But this time, the experiment was different.

Several weeks earlier, the researchers had gently sutured one of the kitten's eyelids shut just a few days after birth. Neither the cornea, nor the retina, nor the optic nerve had been damaged; only light was prevented from entering that eye. Now it was time to open the eyelid.

The eye looked completely healthy. The cornea was clear. The retina was healthy. The optic nerve was also undamaged.

If you looked only at the eye's appearance, you would think that both eyes could see equally well. But Hubel and Wiesel wanted to ask the brain itself a question.

First, they left the healthy eye open and covered the other eye. The loudspeaker immediately came alive.

"Tick... tick... tick... tick..."

The neurons fired one after another.

Now they switched the eyes. The eye that had been closed for several weeks was opened.

Everyone expected to hear the same sounds.

But...

Silence. Only an occasional weak discharge. As if that eye did not exist at all.

At first, Hubel and Wiesel thought that perhaps the eye had been damaged. But examination showed that the eye was completely healthy.

So where was the problem?

The answer lay in the brain itself. During the first weeks of life, neurons in the visual cortex are still forming their connections.

During this critical period, each neuron is like a child who must decide which eye to "listen to." When both eyes receive natural visual input, these connections are distributed almost equally between the two eyes. But in this kitten, only one eye was active.

For weeks, the brain's neurons had received signals only from that eye. As a result, the neural connections associated with the open eye became stronger day by day, while the connections associated with the closed eye, the closed eye, which received no visual inputs, gradually weakened and were eliminated.

When the eyelid was opened several weeks later, it was already too late.

The eye was healthy...



But the brain had no longer learned to use it.

To make sure, Hubel and Wiesel repeated the same experiment in adult cats as well. This time, opening the eyelid produced a completely different result. After several weeks of closing one eye, the cats still responded to both eyes almost as before. The adult brain was no longer nearly as capable of modifying the organization of its visual cortical neurons. At that moment, one of the most fundamental principles of neuroscience became clear:

"For normal development, the brain depends, occur, the brain depends not only on genes, but also on experience. An eye can be completely healthy, but if the brain loses the opportunity to learn to see at the appropriate time (the critical period), normal vision will never fully develop."

This experiment showed that the brain, contrary to the prevailing view at the time, is not a fixed and immutable structure. Hubel and Wiesel demonstrated that experience can shape neural circuits; neurons that receive more input strengthen their connections, while neurons deprived of experience gradually lose some or all of their capabilities.

These studies provided important experimental evidence for the role of experience in the formation of sensory circuits [1, 2].

From Harvard to MIT; 60 Years of Searching to Understand How the Brain Learns

But alongside their major answer, Hubel and Wiesel also left a larger mystery for future generations of scientists.

If experience changes the brain, exactly where does this change occur?

When we remember the face of a new colleague, or learn to recognize a species of bird, a new car model, or even a medical image faster than before, exactly which part of the brain is changing?

Every time we learn something new, are the visual circuits being rewired from scratch? Or has the brain found a more subtle and intelligent way to learn?

This question remained unanswered for more than 60 years. During these years, technologies for recording neuronal activity, brain-imaging methods, and computational neuroscience advanced at a remarkable pace; yet the answer to this question remained unclear.

Until the summer of 2026, when a team of

researchers from the McGovern Institute for Brain Research at MIT, together with collaborators at York University in Toronto, published a study in the prestigious journal *Nature Communications* that once again continued the story from where Hubel and Wiesel had stopped [3].

But this time, their question was no longer, “Does experience change the brain?” Everyone already knew the answer to that question. The new question was:

“Exactly what does the brain change while learning?”

Lin Sörensen (a postdoctoral researcher at McGovern), James DiCarlo (a professor and senior researcher at MIT), and Kohitij Kar (an assistant professor at York University) [3] examined the activity of neurons in a brain region called the inferior temporal cortex (IT), a region that can be considered the final station in the brain’s object-recognition pathway [3].

It is in this region that, after integrating information about lines, colors, edges, and shapes, colors, edges, and shapes, the brain finally recognizes: “This is an elephant,” “This is a chair,” or “This is a human face.”

The scientists recorded activity in the IT cortex of two groups of monkeys: one group that had never been trained and for which the images they saw were almost meaningless, and another group that had practiced for weeks to correctly recognize new objects, even when they appeared at different sizes, angles, and against different backgrounds.

Nevertheless, when neuronal activity was analyzed using much more precise methods, subtle but persistent differences emerged. IT neurons in trained monkeys encoded the objects the animals had learned somewhat differently; as if the brain did not need to destroy and rebuild its architecture in order to learn, but only to make subtle adjustments to what was already there.

When They Built Several “Digital Brains”...

The researchers did not search for the answer to their question only in monkey brains. They went a step further—a step that Hubel and Wiesel in the 1960s could not even have imagined.

“If we could build a brain from scratch, could we watch, moment by moment, exactly which neurons and which circuits change during learning?”

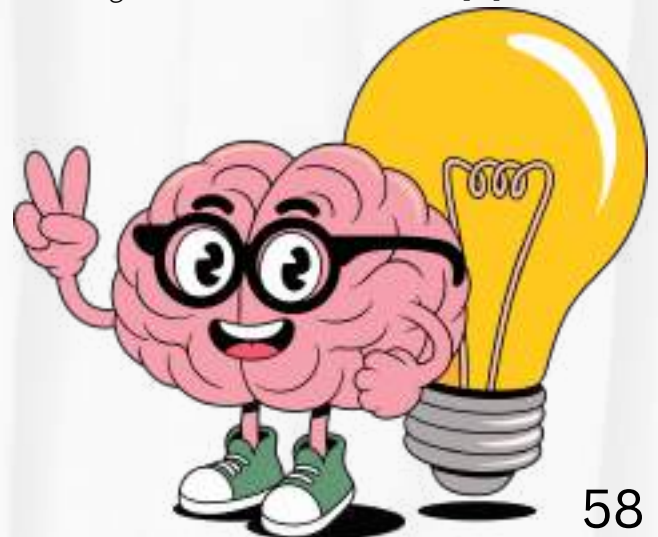
For this purpose, Sörensen designed and trained not one but a collection of artificial neural networks whose architecture was inspired by the visual pathway of the mammalian brain, with their internal components mapped onto the monkey’s IT cortex. Like the real brain, these networks processed images step by step, from extracting simple features such as edges and lines to reaching a layer that played a role similar to the IT cortex—the same region that in the real brain is responsible for representing object identity.

Then the same categories of objects that the monkeys had seen were presented to these networks as well. The models were trained using gradient descent; that is, with every error, their internal parameters were adjusted slightly. They saw the image again, tried again, and learned from their errors. This cycle was repeated thousands of times until the training was complete.

Here there is an important point: gradient descent, in the conventional form used in artificial neural networks, is not considered a direct model of a known biological learning mechanism in the brain. The brain learns in a different way. However, the researchers were not trying to prove that the brain works exactly this way; they wanted to see whether such abstract models could predict the pattern of changes in the real brain.

And the result was interesting: among the set of networks that were trained, only some of those whose architecture resembled that of mammals showed a learning pattern similar to that of real monkeys. In those successful models, the layer that played the role of the IT cortex showed exactly the same kind of subtle changes that the researchers had previously observed in the brains of trained monkeys.

This finding suggested that learning-related changes occur not in the visual system itself, but in circuits downstream of it—circuits that interpret visual information and make decisions based on it. According to Kohitij Kar, one of the authors of the study, this finding suggests that the gap between the region from which the recordings were made and the final behavior is filled with changes that should be investigated in future research [4].



Hubel and Wiesel showed the world that experience can change the brain; but today, this research provides a more precise picture of how neural representations in the IT cortex change after learning objects and also highlights the possible role of downstream circuits.

Sixty years ago, the answer to this question emerged from the “tick... tick... tick...” of a kitten’s neurons. Today, the same story continues at the heart of artificial neural networks.

Perhaps this is the most beautiful feature of science: every discovery is not the end of a story, but the beginning of a question that the next generation of scientists will continue to pursue.



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AN AUTOPSY OF CAPTIVITY: A NARRATIVE OF
CONSCIOUSNESS IMPRISONED WITHIN THE BODY

A NEUROPHYSIOLOGICAL
INTRODUCTION AND
CRITIQUE OF

The Diving Bell and the Butterfly

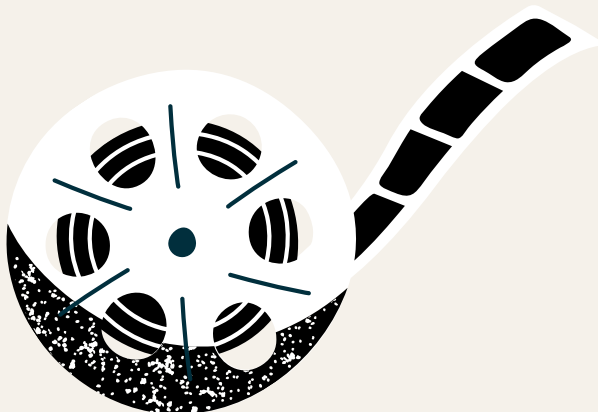
My body had become a
heavy diving suit, but my
mind continued to fly freely
".like a butterfly
Jean-Dominique Bauby

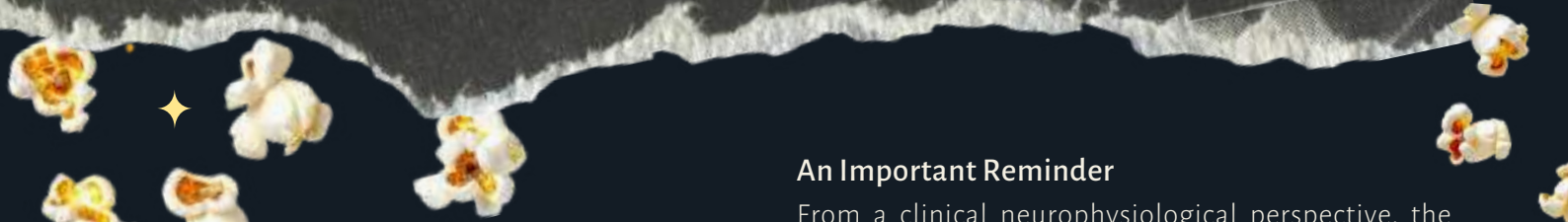
About the Film

The Diving Bell and the Butterfly (2007), directed by Julian Schnabel, is one of the most accurate and compelling cinematic portrayals of Locked-in Syndrome (LIS). Based on the true story of Jean-Dominique Bauby, a French journalist, the film goes beyond the dramatic aspects of the disorder and attempts to convey the subjective and perceptual experience of an individual living with this condition. This distinctive approach makes the film particularly valuable for those interested in neuroscience and neurophysiology. One of the film's greatest strengths is its portrayal of the fact that, contrary to common assumptions, wakefulness and awareness are generally preserved in classic locked-in syndrome, and many cognitive functions may remain relatively intact. Severe damage to the descending motor pathways profoundly limits or disrupts voluntary movements of the limbs and face, as well as speech. Consequently, the patients may be unable to move their limbs or speak, while remaining fully capable of perceiving their surroundings, understanding conversations, and experiencing emotions. This contrast between an active mind and an incapacitated body represents one of the most significant clinical and ethical challenges faced by these patients, and the film portrays it in a remarkably tangible way.

The Anatomy of a Broken Bridge: A Neurophysiological Perspective

From a neurophysiological perspective, Locked-in Syndrome is mostly caused by damage to the ventral pons. The most frequent cause is an ischemic stroke resulting from occlusion of the basilar artery, although trauma, hemorrhage, tumors, and, in some cases, demyelinating diseases can also imitate this clinical presentation. In this condition, descending motor pathways, including the corticospinal and corticobulbar tracts, which transmit motor commands to the limbs and face, are damaged. However, the Ascending Reticular Activating System (ARAS), which is responsible for maintaining wakefulness and consciousness, generally remains intact. As a result, the patient is awake and conscious but unable to produce meaningful motor responses [1].





The Diagnostic Challenge: Differentiating Locked-in Syndrome from Disorders of Consciousness

One noteworthy aspect of the film is its avoidance of an exaggerated or unrealistic portrayal of the disorder. In many cinematic representations, severe physical disability is accompanied by reduced consciousness or cognitive impairment, whereas Locked-in Syndrome is essentially characterized by the opposite situation.

This distinction highlights the critical importance of accurate diagnosis in clinical settings, as a patient with LIS may initially be mistaken for someone in a coma or a vegetative state [2]. Differentiating these conditions requires an accurate neurological examination, assessment of eye movements, and, when necessary, electrophysiological investigations and neuroimaging.

From Blinking to Brain-Computer Interfaces (BCIs)

By adopting a first-person perspective, the film places the audience in a position where they can experience, to some extent, the patient's profound communication limitations. This narrative approach underscores the importance of establishing effective communication with individuals living with LIS.

In clinical practice, many of these patients can communicate through vertical eye movements or blinking. Today, Brain-Computer Interface (BCI) technologies are also providing new possibilities for enhancing the independence of these individuals. Such technologies may allow patients to select letters on a display or control external devices without requiring even a small voluntary body movement.

The film therefore serves as a powerful reminder, particularly for neuroscience students, of the clinical importance and human impact of research into these technologies.

An Important Reminder

From a clinical neurophysiological perspective, the film highlights the importance of accurately assessing the level of consciousness in patients with brain injuries. Silence does not necessarily mean an absence of thought.

Before making any judgment about a patient's level of consciousness, we must search for the "butterfly" trapped within the "diving bell" of physical incapacity.

Film Information Box

- Title: The Diving Bell and the Butterfly
- Director: Julian Schnabel
- Awards: Winner of a Golden Globe and nominated for four Academy Awards
- Running time: 112 minutes

Why Should We Watch This Film?

- For physiology and neuroscience students: To gain a practical understanding of the role of the pons and the descending motor pathways.
- For rehabilitation students: To understand the importance of modern communication strategies for patients with severe physical disabilities.
- For neuroscience researchers: To gain inspiration for research into brain-computer interfaces and the study of consciousness.

References

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2. Giacino, J. T., Ashwal, S., Childs, N., et al. (2002). The minimally conscious state: Definition and diagnostic criteria. *Neurology*, 58(3), 349–353.



Introducing

The Man Who Mistook His Wife for a Hat

**From Clinical Narratives to Understanding
the Brain's Neural Networks**

Compiled by: Maryam Fallahi



In neuroscience education, students are often introduced to concepts such as action potentials, synaptic transmission, cortical circuits, and functional brain networks. Although these concepts form the foundation for understanding the function of the nervous system, their connection to patients' lived experiences is sometimes overlooked.

The Man Who Mistook His Wife for a Hat, by Oliver Sacks, is a well-known example of the connection between clinical narrative and neurology. Despite the fact that several decades have passed since its publication, the book remains an inspiring resource for students of neurology, neurophysiology, and cognitive science.

In this book, Sacks presents a collection of patients with rare neurological disorders. Each patient has lost some aspect of brain function while, at the same time, finding ways to adapt to their condition. The scientific value of these narratives lies in the fact that each clinical case can serve as a kind of natural experiment, providing clues about the relationship between neurological damage and cognitive function.

Damage to a particular brain region or neural network provides an opportunity to investigate its role in perception, memory, language, movement, and identity—an approach that remains one of the foundations of clinical neurology.

Visual Agnosia: The Mystery of the Ventral Stream

The most famous case in the book concerns a patient with visual agnosia. In this disorder, visual information is transmitted normally from the eyes to the primary visual cortex, but the brain is unable to interpret the meaning of what is being seen.

From a neurophysiological perspective, this phenomenon highlights the importance of the ventral visual stream, a network involved in the recognition of objects and faces. This example demonstrates that perception is not the product of activity within a single brain center; rather, it emerges from dynamic interactions among multiple cortical and subcortical regions.

The Language of Brain Waves

This perspective is fully consistent with findings from contemporary neuroscience. Today, using techniques such as local field potential (LFP) recording, electroencephalography (EEG), magnetoencephalography (MEG), and functional magnetic resonance imaging (fMRI), researchers have established that information processing in the brain relies on the coordinated activity of neural networks.

Neural oscillations across different frequency bands are associated with various forms of cognitive processing and the coordination of neuronal populations. However, their specific role depends on the network involved, the task being performed, and the experimental context.

This perspective is particularly important for electrophysiology researchers. In studies involving LFP recordings, especially in animal models, researchers seek to understand how the activity of neuronal populations is related to learning, memory, and perception.

Although modern technologies have advanced dramatically since Sacks's time, the fundamental question remains the same:

How does the activity of millions of neurons become transformed into conscious human experience?





Neuroplasticity: Mechanisms of Adaptation and Survival

Another important theme of the book is the concept of neuroplasticity. Despite structural damage, many of the patients described by Sacks have been able to adapt by relying on the remaining capacities of their brains and have developed strategies that allow them to continue living their lives.

Research over the past two decades has shown that such adaptation can involve changes in synaptic strength, reorganization of functional networks, and alterations in patterns of brain oscillations. These processes now constitute major areas of research into long-term potentiation (LTP), long-term depression (LTD), and neurological rehabilitation.

At the same time, the book serves as a reminder of the limitations of viewing neuroscience purely through an experimental lens. Recording a waveform in an EEG, observing a change in LFP amplitude, or detecting alterations in neuronal activity only becomes truly meaningful when we understand how these changes affect a patient's quality of life.

Sacks's narratives beautifully bridge the gap between laboratory data and clinical reality. They demonstrate that, in human studies, the interpretation of electrophysiological signals becomes more meaningful when those signals are considered in relation to behavior, clinical status, and the individual's subjective experience.

The Human Being Behind the Signal

Perhaps the most important message of the book for neurophysiology researchers is that understanding the brain cannot be achieved through the study of neurons alone. The interactions among neural circuits, cognition, behavior, and the environment must also be taken into account.

This is precisely the approach pursued today in Network Neuroscience, and it underlies much of the advanced research involving LFP recordings, brain-computer interfaces, and computational modeling of neural activity.

From this perspective, *The Man Who Mistook His Wife for a Hat* is not merely a collection of stories or clinical case reports. Rather, it is a valuable reminder that behind every graph, every recorded waveform, and every electrophysiological dataset, there is a human being with a unique experience.

Perhaps it is this humanistic perspective that has allowed the book, more than four decades after its publication, to remain one of the most engaging and thought-provoking works for those interested in neuroscience.

The Book Is Organized into Four Main Sections:

1. Losses:

Exploring neurological deficits and losses, such as agnosia, aphasia, and memory loss.

2. Excesses:

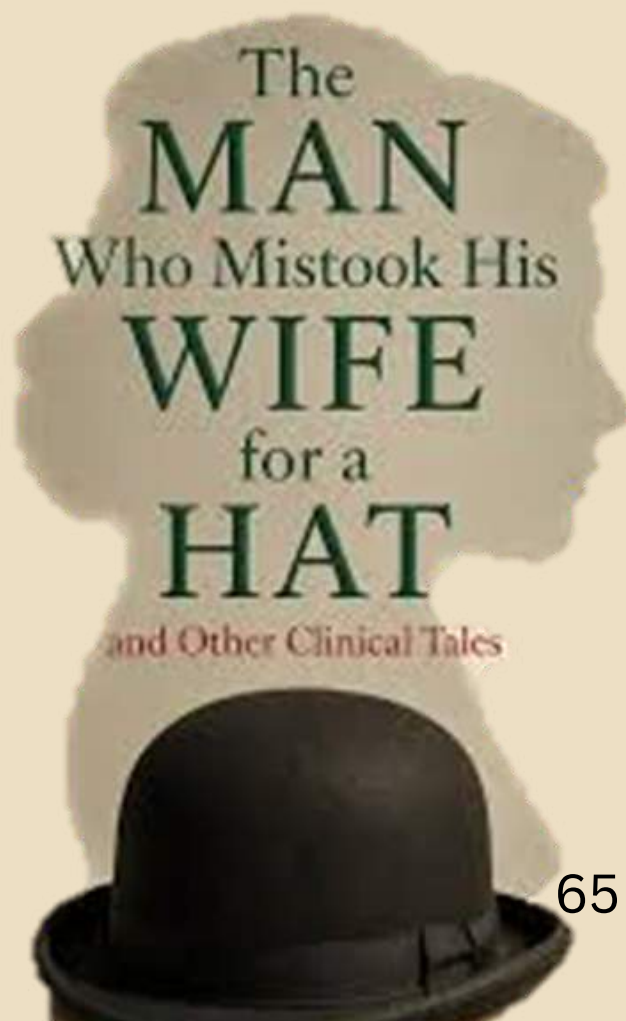
Focusing on excessive or abnormal brain activity, including conditions such as Tourette syndrome.

3. Transports:

Exploring dream-like experiences, hallucinations, and perceptual alterations resulting from neurological disorders.

4. The World of the Simple:

Focusing on patients with intellectual disabilities or autism who possess remarkable and hidden abilities, including savant syndrome.



The Book in the Iranian Publishing Market

Fortunately, this remarkable work has also received considerable attention in Iran. It has been translated and published in Iran under the title *The Man Who Mistook His Wife for a Hat* by Mandana Farhadian, through Nashr-e Now.

Another translation of the same book, published under the title *The Lady Without a Body* (Bānu-y-e Bi-Badan), was translated by Sama Charayi and published by Chatreh Publishing.

For students and enthusiasts of neuroscience and neurophysiology, reading both translations can provide an opportunity to compare different approaches to Sacks's distinctive clinical narratives.



**"TODAY A READER,
TOMORROW A LEADER"**

Neurophysiology Journal

We hope that the writing of this publication and the unceasing efforts of the editorial board members and scientific collaborators to prepare this issue will be a useful step toward enhancing your knowledge in the field of neurophysiology.

It should be noted that in writing and compiling this collection, depending on the authors' discretion, modifications have been made to the original compiled or translated material.

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