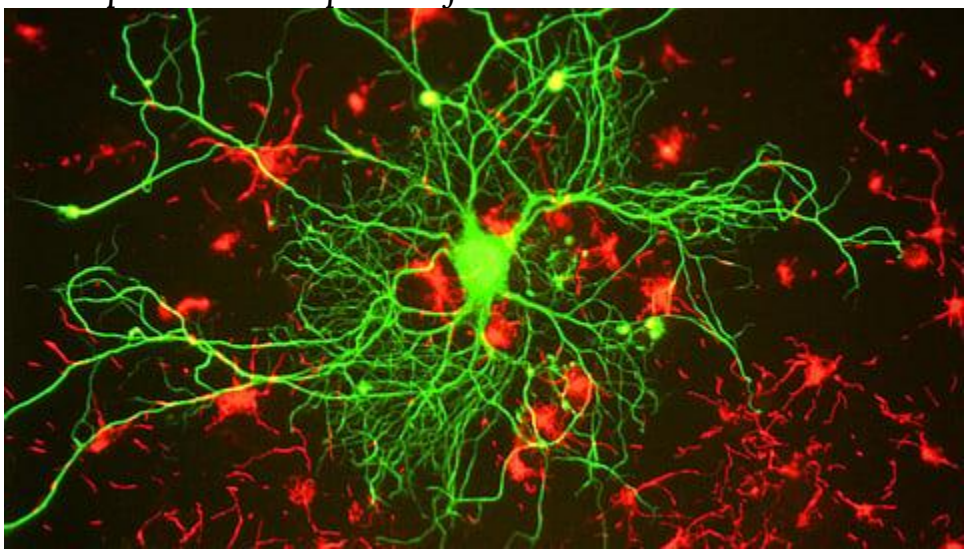
Calcium-mediated dendritic action potentials (dCaAPs)

Recent research has revealed a **unique type of electrical signal** in the human brain, known as **calcium-mediated dendritic action potentials (dCaAPs)**. This discovery focuses on dendrites, the branch-like extensions of neurons, and indicates that these signals exhibit a **graded response**, meaning their strength varies with input intensity. Unlike typical all-or-none responses, dCaAPs allow individual neurons to process complex information independently, challenging previous beliefs about how neural networks function. This finding opens new avenues for understanding brain computation and cognition, highlighting the sophistication of the human brain compared to other animals.

Groundbreaking Discovery of Unique Electrical Signals in the Human Brain

New research reveals distinct brain signals in dendrites, redefining how neurons process complex information



Newly discovered brain signals reveal the human brain's unmatched computational abilities. (Representational image: Wikimedia Commons)

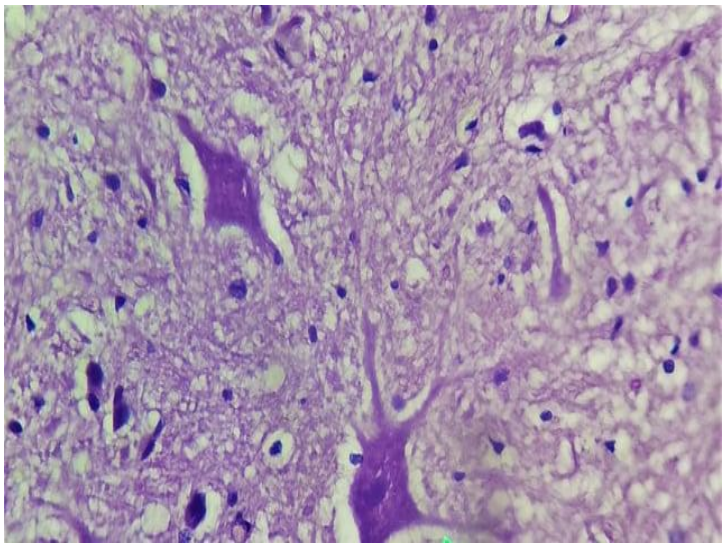
For the first time, researchers have identified a unique type of electrical signal in the human brain, providing new insights into how information is processed. This breakthrough focuses on dendrites, the branch-like extensions of neurons responsible for receiving and transmitting signals. While previous studies on dendritic electrical activity were primarily conducted on rodents, this research examined human brain tissue, specifically from layer 2/3 (L2/3) pyramidal neurons in the cerebral cortex. This region is known for its vital role in advanced thinking and problem-solving.

Dendrites are crucial components of neurons, acting as the main receivers of signals from other nerve cells. These signals are transmitted to the neuron's soma, or main body, where they are further processed. Understanding dendritic activity has been a central focus in neuroscience, but the findings from this study have revealed entirely new dynamics in human neurons.

Discovery of a New Signal

A previously unknown type of electrical signal, referred to as calcium-mediated dendritic action potentials (dCaAPs), was discovered during the study. Unlike the typical "all-or-none" responses that are standard in neuronal signaling, these dCaAPs exhibited a "graded" response. The strength of these signals varied based on the level of input, reaching maximum efficiency with moderate stimulation but diminishing when stronger inputs were applied.

This discovery challenges traditional views of neural communication. While it was previously believed that complex problems required the involvement of entire networks of neurons, the study demonstrated that individual neurons, through these unique dendritic signals, can process intricate information independently. Essentially, a single neuron is capable of classifying and interpreting inputs that were once thought to be beyond the capacity of a single cell.



Unique dendritic signals challenge traditional views on neuron networks and brain function. (Representational image: Wikimedia Commons)

Implications for Brain Function

The findings highlight the advanced computational abilities of human neurons, distinguishing them from those of other species. Researchers suggest that these distinctive dendritic properties may contribute to the human brain's remarkable cognitive abilities, including problem-solving and abstract thought. This study challenges long-standing assumptions about the function of neural networks, emphasizing the sophistication of human brain activity.

Applications in Neurological Research

Beyond deepening the understanding of brain computation, the discovery opens new doors for exploring neurological disorders. Many conditions, such as Alzheimer's disease, epilepsy, and autism, involve disruptions in how the brain processes information. By understanding the role of these unique signals in healthy brain function, researchers can better explore how their dysfunction contributes to such disorders.

This groundbreaking research also offers potential for developing targeted therapies. Insights into how neurons independently process complex information could inspire new treatments for neurological conditions where brain computation fails.

The identification of calcium-mediated dendritic action potentials in the human brain marks a significant advancement in neuroscience. This discovery not only enhances our understanding of human brain function but also underscores the complexity and uniqueness of human cognition. By further studying these signals, scientists may uncover new ways to address neurological disorders, advancing both our knowledge of the brain and our ability to treat its ailments.

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Brain Cells Use Muscle-Like Signals to Strengthen Learning and Memory

·February 7, 2025

Summary: New research reveals that brain cells use a muscle-like signaling mechanism to relay information over long distances. Scientists discovered that dendrites, the branch-like extensions of neurons, contain a structured network of contact sites that amplify calcium signals—similar to how muscles contract. These contact sites

regulate calcium release, activating key proteins involved in learning and memory.

This mechanism explains how neurons process information received at specific points and relay it to the cell body. Understanding this process sheds light on synaptic plasticity, which underlies learning and memory formation. The findings could provide new insights into neurodegenerative diseases like Alzheimer's.

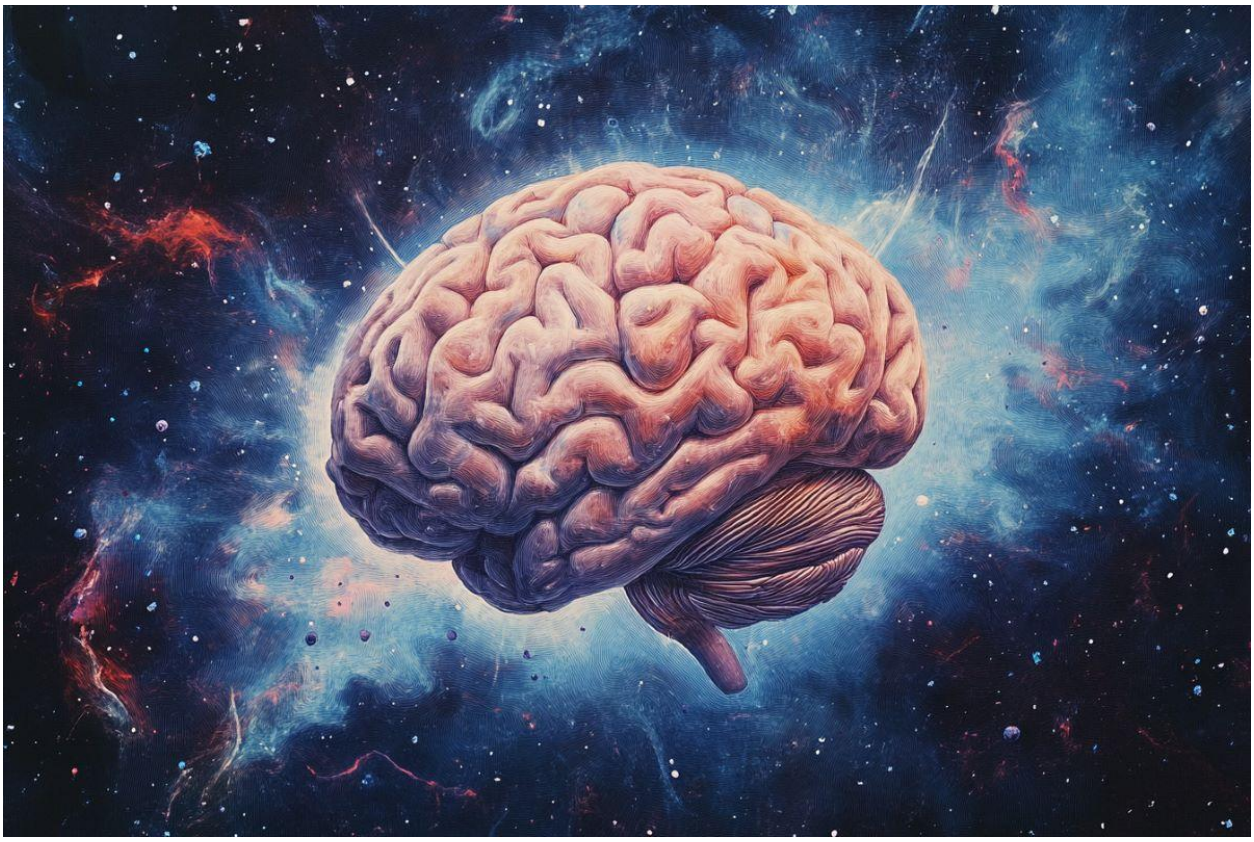
Key Facts:

- **Neural Calcium Amplification:** Brain cells use structured ER contact sites to amplify calcium signals, similar to how muscle cells trigger contractions.
- **Memory and Learning Connection:** These calcium signals activate CaMKII, a protein critical for strengthening neuronal connections and memory formation.
- **Potential Disease Insights:** Understanding this mechanism could help explain cognitive dysfunction in conditions like Alzheimer's disease.

Source: HHMI

Our biceps and our brain cells may have more in common than previously thought.

New research led by the Lippincott-Schwartz Lab shows that a network of subcellular structures similar to those responsible for propagating molecular signals that make muscles contract are also responsible for transmitting signals in the brain that may facilitate learning and memory.



This process continues from contact site to contact site all along the dendrite to the cell body, where the neuron decides how it will communicate with other neurons. Credit: Neuroscience News

“Einstein said that when he uses his brain, it is like he is using a muscle, and in that respect, there is some parallel here,” says Janelia Senior Group Leader Jennifer Lippincott-Schwartz.

“The same machinery is operating in both cases but with different readouts.”

The first clue about the possible connection between brain and muscle cells came when Janelia scientists noticed something strange about the endoplasmic reticulum, or ER – the membranous sheets and folds inside cells that are crucial for many cellular functions.

Lorena Benedetti, a research scientist in the Lippincott-Schwartz Lab, was tracking molecules at high resolution along the surface of the ER in mammalian neurons when she saw that the molecules were tracing a

repeating, ladder-like pattern along the entire length of the dendrites — the branch-like extensions on brain cells that receive incoming signals.

Around the same time, Senior Group Leader Stephan Saalfeld alerted Lippincott-Schwartz to high-resolution 3D electron microscopy images of neurons in the fly brain where the ER was also forming regularly spaced, transversal structures.

The ER normally appears like a huge, dynamic net, so as soon as Lippincott-Schwartz saw the structures, she knew her lab needed to figure out what they were for.

“In science, structure is function,” says Lippincott-Schwartz, who also heads Janelia’s 4D Cellular Physiology research area.

“This is an unusual, beautiful structure that we are seeing throughout the whole dendrite, so we just had this feeling that it must have some important function.”

The researchers, led by Benedetti, started by looking at the only other area of the body known to have similar, ladder-like ER structures: muscle tissue.

In muscle cells, the ER and the plasma membrane – the outer membrane of the cell – meet at periodic contact sites, an arrangement controlled by a molecule called junctophilin.

Using high-resolution imaging, the researchers discovered that dendrites also contain a form of junctophilin that controls contact sites between their ER and plasma membrane.

Further, the team found that the same molecular machinery controlling calcium release at muscle cells’ contact sites — where calcium drives muscle contraction — was also present at dendrite contact sites — where calcium regulates neuronal signaling.

Because of these clues, the researchers had a hunch that the molecular machinery at the dendritic contact sites must also be important for transmitting calcium signals, which cells use to communicate.

They suspected that the contact sites along the dendrites might act like a repeater on a telegraph machine: receiving, amplifying, and propagating signals over long distances. In neurons, this could explain how signals received at specific sites on dendrites are relayed to the cell body hundreds of micrometers away.

“How that information travels over long distances and how the calcium signal gets specifically amplified was not known,” says Benedetti.

“We thought that ER could play that role, and that these regularly distributed contact sites are spatially and temporally localized amplifiers: they can receive this calcium signal, locally amplify this calcium signal, and relay this calcium signal over a distance.”

The researchers found that this process is triggered when a neuronal signal causes calcium to enter the dendrite through voltage-gated ion channel proteins, which are positioned at the contact sites. Although this initial calcium signal dissipates quickly, it triggers the release of additional calcium from the ER at the contact site.

This influx of calcium at the contact site attracts and activates a kinase called CaMKII, a protein known to be important in memory. CaMKII alters the plasma membrane’s biochemical properties, changing the strength of the signal that is passed down the plasma membrane.

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It also sheds light on the molecular mechanisms underlying synaptic plasticity – the strengthening or weakening of neuronal connections that enables learning and memory.

Figuring out this process at the molecular level could increase understanding of how the brain works normally and in diseases where these processes go awry, like Alzheimer's.

"We are showing that a structure – a beautiful structure – operating at a level of subcellular organization is having a huge effect on the way the entire neuronal system is operating vis-à-vis calcium signaling," Lippincott-Schwartz says.

"This is a great example of how, in doing science, if you see a beautiful structure, it can take you into a whole new world."

About this learning and memory research news

"Periodic ER-plasma membrane junctions support long-range Ca2+ signal integration in dendrites" by Jennifer Lippincott-Schwartz et al. *Cell*

Abstract

Periodic ER-plasma membrane junctions support long-range Ca2+ signal integration in dendrites

Neuronal dendrites must relay synaptic inputs over long distances, but the mechanisms by which activity-evoked intracellular signals propagate over macroscopic distances remain unclear.

Here, we discovered a system of periodically arranged endoplasmic reticulum-plasma membrane (ER-PM) junctions tiling the plasma membrane of dendrites at ~1 µm intervals, interlinked by a meshwork of ER tubules patterned in a ladder-like array.

Populated with Junctophilin-linked plasma membrane voltage-gated Ca^{2+} channels and ER Ca^{2+}-release channels (ryanodine receptors), ER-PM junctions are hubs for ER-PM crosstalk, fine-tuning of Ca^{2+} homeostasis, and local activation of the Ca^{2+}/calmodulin-dependent protein kinase II.

Local spine stimulation activates the Ca^{2+} modulatory machinery, facilitating signal transmission and ryanodine-receptor-dependent Ca^{2+} release at ER-PM junctions over 20 µm away.

Thus, interconnected ER-PM junctions support signal propagation and Ca^{2+} release from the spine-adjacent ER.

The capacity of this subcellular architecture to modify both local and distant membrane-proximal biochemistry potentially contributes to dendritic computations.

New discovery links brain and muscle cells in signal transmission

*Howard Hughes Medical Institute*Feb 8 2025

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Using high-resolution imaging, the researchers discovered that dendrites also contain a form of junctophilin that controls contact sites between their ER and plasma membrane. Further, the team found that the same molecular machinery controlling calcium release at muscle cells' contact sites - where calcium drives muscle contraction - was also present at dendrite contact sites - where calcium regulates neuronal signaling.

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The researchers found that this process is triggered when a neuronal signal causes calcium to enter the dendrite through voltage-gated ion channel proteins, which are positioned at the contact sites. Although this initial calcium signal dissipates quickly, it triggers the release of additional calcium from the ER at the contact site.

This influx of calcium at the contact site attracts and activates a kinase called CaMKII, a protein known to be important in memory. CaMKII alters the plasma membrane's biochemical properties, changing the strength of the signal that is passed down the plasma membrane.

This process continues from contact site to contact site all along the dendrite to the cell body, where the neuron decides how it will communicate with other neurons.

The new research reveals a novel mechanism for signal transmission in brain cells and helps answer an open question in neuroscience about how intracellular signals travel over long distances in neurons, enabling information received at specific sites on dendrites to be processed in the brain.

It also sheds light on the molecular mechanisms underlying synaptic plasticity – the strengthening or weakening of neuronal connections that enables learning and memory. Figuring out this process at the molecular level could increase understanding of how the brain works normally and in diseases where these processes go awry, like Alzheimer's.

"We are showing that a structure – a beautiful structure – operating at a level of subcellular organization is having a huge effect on the way the entire neuronal system is operating vis-à-vis calcium signaling," Lippincott-Schwartz says. "This is a great example of how, in doing science, if you see a beautiful structure, it can take you into a whole new world."

02/07/25 | From muscle to memory: new research uses clues from the body to understand signaling in the brain

New research shows that how a network of subcellular structures is responsible for transmitting signals in neurons. This movie shows 3D renderings of these structures in high-resolution 3D electron microscopy images of fruit fly neurons. The endoplasmic reticulum (green), plasma membrane (blue), mitochondria (pink), microtubules (tan), and ER-plasma membrane contacts (magenta) are segmented from FIB-SEM datasets of a Drosophila melanogaster MBON1 neuron. *Credit: Benedetti et al.*

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This movie shows time-lapse high-resolution imaging in neurons, revealing the dynamic behavior of ER tubules contrasted with the persistence of ER-PM junctional sites over time. Time-lapse acquired using 2D lattice-SIM in burst mode of HaloTag-Sec61β (labeled with JF585 HaloTag-ligand) expressing neurons. Scale bars: 0.5 µm. *Credit: Benedetti et al.*

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This movie shows high-resolution imaging of neurons, showing lysosomes swiftly moving through ladder-like ER arrays. Time-lapse acquired using Lattice-SIM of mEmerald-Sec61β expressing neurons. Scale bars: 0.5 µm. *Credit: Benedetti et al.*

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Lorena Benedetti, Ruolin Fan, Aubrey V Weigel, Andrew S Moore, Patrick R Houlihan, Mark Kittisopikul, Grace Park, Alyson Petruncio, Philip M Hubbard, Song Pang, C Shan Xu, Harald F Hess, Stephan Saalfeld, Vidhya Rangaraju, David E Clapham, Pietro De Camilli, Timothy A Ryan, Jennifer Lippincott-Schwartz. "Periodic ER-plasma membrane junctions support long-range Ca2+ signal integration in dendrites." PMID: 39708809

A First-of-Its-Kind Signal Has Been Detected in Human Brains

Scientists have identified a unique form of cell messaging occurring in the human brain, revealing just how much we still have to learn about its mysterious inner workings.

Excitingly, the discovery hints that our brains might be even more powerful units of computation than we realized.

In 2020, researchers from institutes in Germany and Greece reported a mechanism in the brain's outer cortical cells that produces a novel 'graded' signal all on its own, one that could provide individual neurons with another way to carry out their logical functions.

By measuring the electrical activity in sections of tissue removed during surgery on epileptic patients and analyzing their structure using fluorescent microscopy, the neurologists found individual cells in the cortex used not just the usual sodium ions to 'fire', but calcium as well.

This combination of positively charged ions kicked off waves of voltage that had never been seen before, referred to as a calcium-mediated dendritic action potentials, or dCaAPs.

Brains – especially those of the human variety – are often compared to computers. The analogy has its limits, but on some levels they perform tasks in similar ways.

Both use the power of an electrical voltage to carry out various operations. In computers it's in the form of a rather simple flow of electrons through intersections called transistors.

In neurons, the signal is in the form of a wave of opening and closing channels that exchange charged particles such as sodium, chloride, and potassium. This pulse of flowing ions is called an action potential.

Instead of transistors, neurons manage these messages chemically at the end of branches called dendrites.

"The dendrites are central to understanding the brain because they are at the core of what determines the computational power of single neurons," Humboldt University neuroscientist Matthew Larkum told Walter Beckwith at the American Association for the Advancement of Science.

Dendrites are the traffic lights of our nervous system. If an action potential is significant enough, it can be passed on to other nerves, which can block or pass on the message.

This is the logical underpinnings of our brain – ripples of voltage that can be communicated collectively in two forms: either an *AND* message (if x *and* y are triggered, the message is passed on); or an *OR* message (if x *or* y is triggered, the message is passed on).

Arguably, nowhere is this more complex than in the dense, wrinkled outer section of the human central nervous system; the cerebral cortex. The deeper second and third layers are especially thick, packed with branches that carry out high order functions we associate with sensation, thought, and motor control.

It was tissues from these layers that the researchers took a close look at, hooking up cells to a device called a somatodendritic patch clamp to send active potentials up and down each neuron, recording their signals.

"There was a 'eureka' moment when we saw the dendritic action potentials for the first time," said Larkum.

To ensure any discoveries weren't unique to people with epilepsy, they double checked their results in a handful of samples taken from brain tumors.

While the team had carried out similar experiments on rats, the kinds of signals they observed buzzing through the human cells were very different.

More importantly, when they dosed the cells with a sodium channel blocker called tetrodotoxin, they still found a signal. Only by blocking calcium did all fall quiet.

Finding an action-potential mediated by calcium is interesting enough. But modelling the way this sensitive new kind of signal worked in the cortex revealed a surprise.

In addition to the logical *AND* and *OR*-type functions, these individual neurons could act as 'exclusive' *OR* (*XOR*) intersections, which only permit a signal when another signal is graded in a particular fashion.

"Traditionally, the *XOR* operation has been thought to require a network solution," the researchers wrote.

More work needs to be done to see how dCaAPs behave across entire neurons, and in a living system. Not to mention whether it's a human-thing, or if similar mechanisms have evolved elsewhere in the animal kingdom.

Technology is also looking to our own nervous system for inspiration on how to develop better hardware; knowing our own individual cells have a few more tricks up their sleeves could lead to new ways to network transistors.

Exactly how this new logic tool squeezed into a single nerve cell translates into higher functions is a question for future researchers to answer.

This research was published in *Science*.

Scientists Uncover a New Signal in Human Brain Cells: A Potential Leap in Understanding Neural Power

The human brain, often described as the most complex organ in the universe, continues to reveal its secrets. In a groundbreaking discovery, scientists have identified a new type of signal within human brain cells that could reshape our understanding of how the brain functions as a computational unit. This new signal, found in cortical cells, suggests that the brain's capabilities might far exceed previous estimations.

The Discovery: A New Wave of Voltage

Researchers have uncovered a unique graded signal within neurons, called a **calcium-mediated dendritic action potential (dCaAP)**. Unlike the traditional action potentials generated by sodium ions, this new signal involves the flow of calcium ions, creating a distinct wave of voltage. This finding challenges the established notion that neuron communication is exclusively governed by sodium-based action potentials.

Key Features of the Discovery:

- **Calcium Ions in Action**: While sodium ions are the main drivers of traditional neural firing, calcium ions play a crucial role in this new signal, adding a layer of complexity to neural computations.
- **Dendritic Involvement**: The signal originates in the dendrites, the branched extensions of neurons that receive information from other cells. This emphasizes the dendrite's active role in information processing, rather than merely acting as a passive conduit.
- **Graded Nature**: Unlike the "all-or-nothing" nature of typical action potentials, this new signal appears to be graded, allowing for more nuanced computational processing.

How the Brain Transmits Information

To appreciate the significance of this discovery, it's essential to understand how neurons traditionally transmit information.

Neurons, the fundamental units of the brain, rely on both **electrical and chemical signals** to communicate.

1. **Electrical Signals (Action Potentials)**:
    - When a neuron receives a stimulus strong enough to cross its threshold, it generates an action potential.
    - This electrical impulse travels along the neuron's axon to its terminal, where it reaches the synapse.
2. **Chemical Signals (Neurotransmitters)**:
    - At the synapse, the action potential triggers the release of neurotransmitters.
    - These chemical messengers cross the synaptic gap and bind to receptors on the receiving neuron, potentially triggering a new action potential.

This seamless interaction of electrical and chemical signals forms the basis of neural communication, allowing the brain to perform complex tasks like thought, memory, emotion, and sensory perception.

Implications of the New Signal

The discovery of calcium-mediated dendritic action potentials could revolutionize our understanding of neural computation. Here's why:

1. **Enhanced Computational Power**:
    - Traditional models of the brain liken neurons to simple computational units that either fire or

remain silent. The graded nature of this new signal suggests a more nuanced system, akin to analog computing, where information processing can be far more sophisticated.

2. **Role of Dendrites**:
    - Dendrites were once thought to be passive structures that simply relay information to the neuron's body. This discovery highlights their active role in generating signals and processing information, potentially making each neuron a more powerful computational unit.
3. **Complex Neural Networks**:
    - Neurons don't work in isolation; they form vast, interconnected networks where each neuron communicates with thousands of others. The discovery of this new signal adds another layer of complexity to these networks, indicating that the brain's information-processing capabilities may be significantly underestimated.
4. **Bridging Biology and Technology**:
    - Both brains and computers rely on electrical voltage for operations. However, while computers use transistors, the brain uses action potentials and now, possibly, graded dendritic signals. This discovery could inspire advancements in artificial intelligence and neuromorphic computing, where systems are designed to mimic the brain's computational processes.

How This Discovery Differs from Traditional Brain Signals

Traditional action potentials operate on an **all-or-nothing principle**: a neuron either fires or it doesn't. This binary mode of operation is efficient for basic communication but limits the complexity of computations a single neuron can perform.

The newly discovered signal is **graded**, meaning it can vary in intensity, allowing for more intricate information processing. This is akin to comparing a digital system (binary) to an analog system (continuous). The analog nature of the new signal could enable neurons to perform more complex computations independently, reducing the reliance on larger networks for processing.

What This Means for Brain Research

The discovery of calcium-mediated dendritic action potentials opens several avenues for research and application:

1. **Advancing Neurological Studies**:
    - Understanding this new signal could provide insights into brain disorders where neural communication is disrupted, such as epilepsy, Alzheimer's disease, or autism.
2. **Improving AI and Neuromorphic Computing**:
    - By studying how neurons use this new signal, scientists can develop better algorithms and hardware for artificial intelligence, bringing it closer to mimicking human thought processes.
3. **Revisiting Neural Models**:

- Many existing models of brain function will need to be revised to incorporate this new form of neural signaling, potentially leading to a more accurate understanding of how the brain works.

A Deeper Look into Neural Networks

Neurons form intricate networks where a single neuron can send and receive signals from thousands of others. This creates a vast web of connections that allows the brain to process, store, and transmit information at astonishing speeds.

The discovery of calcium-mediated dendritic action potentials adds another layer to this complexity. It suggests that dendrites, which were previously thought to simply transmit incoming signals to the neuron's body, can independently generate their own signals. This could mean that the brain has an untapped reserve of computational power that researchers are only beginning to understand.

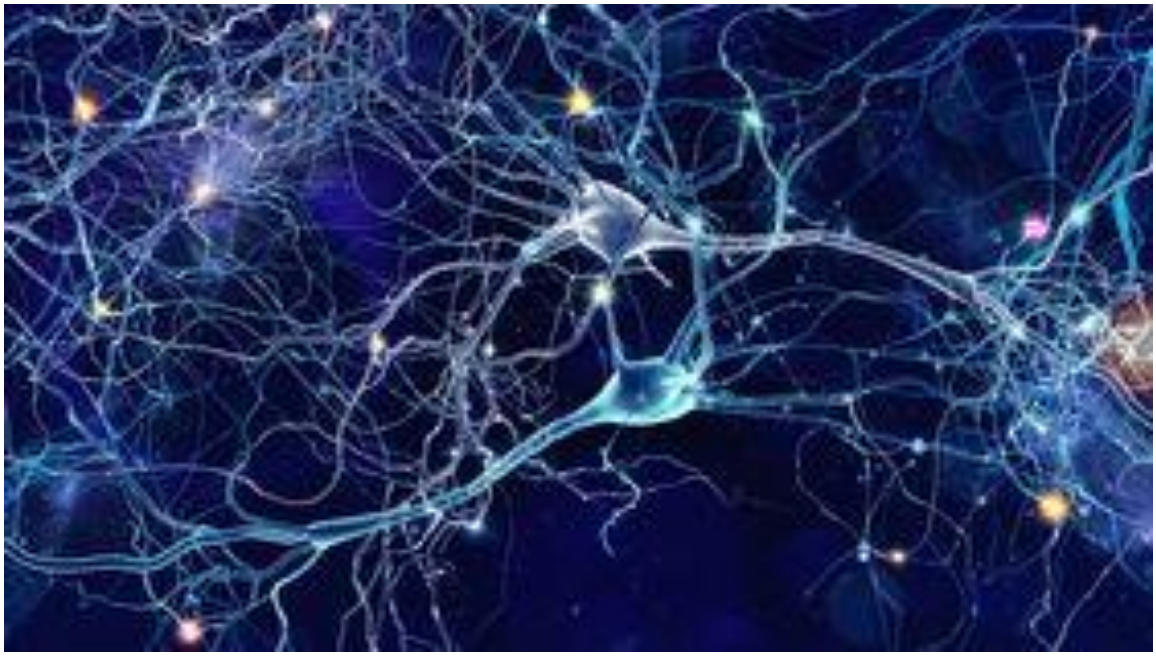
Conclusion: A New Frontier in Neuroscience

The discovery of a new type of signal in human brain cells is a monumental step forward in neuroscience. It challenges long-standing assumptions about how neurons function and opens up exciting possibilities for understanding the brain's true computational power. By shedding light on the role of dendrites and the graded nature of this new signal, scientists are uncovering

a more intricate picture of how our brains process and transmit information.

This breakthrough not only enhances our understanding of the human brain but also holds the potential to influence fields as diverse as medicine, artificial intelligence, and cognitive science. As research continues, this discovery may lead to new technologies, therapies, and insights into what makes the human brain the remarkable organ it is.

Scientists Have Discovered A New Kind of Signal in the Human Brain



Conceptual image of neurons firing in the brain. whitehoune/Shutterstock

Neuroscientists have discovered a new signal process in the brain that they suggest may be key to what makes us human.

The human brain is a complex system of cells called neurons that exchange information using electrical and chemical signals. In a new study published in Science, researchers found that certain cells in the human brain transmit signals in a way not seen in corresponding rodent cells.

Demonstrable differences in human compared to other mammal brains helps us pin down why human brains may be unique, which can lead to a better understanding, and even better modeling, of our brains.

The researchers looked at slices of brains from patients who had either epilepsy or tumors. They focused on the dendrites – the branch-like extensions of brain cells that connect to other brain cells, allowing information to be exchanged – in the second and third layers of the brain's cortex (outermost layer).

Most of what we know about dendrites is from rodent studies, so the opportunity to study human samples is vital. Patients with epilepsy were chosen due to epilepsy surgeries providing enough cortex tissue to analyze, and the tumor samples were to ensure that the results weren't only found in those with epilepsy.

Thanks to the human brain's expansion as we evolved, it has an unusually thick cortex (around 3 millimeters), which is disproportionately thick in the second and third layers, leading to large and elaborate dendrite trees.

The synapse is a structure that allows electric nerve impulses to be sent between two neurons. Neurons communicate via electrical events called "action potentials" – a burst of electrical activity when a neuron sends information away from the cell. Hundreds of synaptic inputs to a neuron determine whether an action potential results. The active electrical properties of these dendrites determine the numerous transformations from synaptic input to action potential, which means they are key to a neuron's computational power.

The team used a patch clamp to construct an electrical circuit for the cells and a fluorescing imaging technique to investigate the properties of the cells. They discovered previously unknown classes of action potentials in the dendrites of these neurons, which means their activity is much more complex than previously realized.

Among the revelations, the researchers noted that one of the new kinds of action potentials traveled using just calcium ions, instead of both calcium and sodium ions, something not seen before in mammal cortex cells.

They studied the behavior of the action potentials by creating a computer-simulated model and discovered another surprising aspect – they could perform a "computational" function that researchers had previously thought required an entire network of neurons, not just one. From muscle to memory: New research uses clues from the body to understand signaling in the brain February 9, 2025

Howard Hughes Medical Institute

New research shows that a network of subcellular structures similar to those responsible for propagating molecular signals that make muscles contract are also responsible for transmitting signals in the brain that may facilitate learning and memory.

Our biceps and our brain cells may have more in common than previously thought.

New research led by the Lippincott-Schwartz Lab shows that a network of subcellular structures similar to those responsible for propagating molecular signals that make muscles contract are also responsible for transmitting signals in the brain that may facilitate learning and memory.

"Einstein said that when he uses his brain, it is like he is using a muscle, and in that respect, there is some parallel here," says Janelia Senior Group Leader Jennifer Lippincott-Schwartz. "The same machinery is operating in both cases but with different readouts."

The first clue about the possible connection between brain and muscle cells came when Janelia scientists noticed something strange about the endoplasmic reticulum, or ER -- the membranous sheets and folds inside cells that are crucial for many cellular functions.

Lorena Benedetti, a research scientist in the Lippincott-Schwartz Lab, was tracking molecules at high resolution along the surface of the ER in mammalian neurons when she saw that the molecules were tracing a repeating, ladder-like pattern along the entire length of the dendrites -- the branch-like extensions on brain cells that receive incoming signals.

Around the same time, Senior Group Leader Stephan Saalfeld alerted Lippincott-Schwartz to high-resolution 3D electron microscopy images of neurons in the fly brain where the ER was also forming regularly spaced, transversal structures.

The ER normally appears like a huge, dynamic net, so as soon as Lippincott-Schwartz saw the structures, she knew her lab needed to figure out what they were for.

"In science, structure is function," says Lippincott-Schwartz, who also heads Janelia's 4D Cellular Physiology research area. "This is an unusual, beautiful structure that we are seeing throughout the whole dendrite, so we just had this feeling that it must have some important function."

The researchers, led by Benedetti, started by looking at the only other area of the body known to have similar, ladder-like ER structures: muscle tissue. In muscle cells, the ER and the plasma membrane -- the outer membrane of the cell -- meet at periodic contact sites, an arrangement controlled by a molecule called junctophilin.

Using high-resolution imaging, the researchers discovered that dendrites also contain a form of junctophilin that controls contact sites between their ER and plasma membrane. Further, the team found that the same molecular machinery controlling calcium release at muscle cells' contact sites -- where calcium drives muscle contraction -- was also present at dendrite contact sites -- where calcium regulates neuronal signaling.

Because of these clues, the researchers had a hunch that the molecular machinery at the dendritic contact sites must also be important for transmitting calcium signals, which cells use to communicate. They suspected that the contact sites along the dendrites might act like a

repeater on a telegraph machine: receiving, amplifying, and propagating signals over long distances. In neurons, this could explain how signals received at specific sites on dendrites are relayed to the cell body hundreds of micrometers away.

"How that information travels over long distances and how the calcium signal gets specifically amplified was not known," says Benedetti. "We thought that ER could play that role, and that these regularly distributed contact sites are spatially and temporally localized amplifiers: they can receive this calcium signal, locally amplify this calcium signal, and relay this calcium signal over a distance."

The researchers found that this process is triggered when a neuronal signal causes calcium to enter the dendrite through voltage-gated ion channel proteins, which are positioned at the contact sites. Although this initial calcium signal dissipates quickly, it triggers the release of additional calcium from the ER at the contact site. This influx of calcium at the contact site attracts and activates a kinase called CaMKII, a protein known to be important in memory. CaMKII alters the plasma membrane's biochemical properties, changing the strength of the signal that is passed down the plasma membrane. This process continues from contact site to contact site all along the dendrite to the cell body, where the neuron decides how it will communicate with other neurons.

The new research reveals a novel mechanism for signal transmission in brain cells and helps answer an open question in neuroscience about how intracellular signals travel over long distances in neurons, enabling information received at specific sites on dendrites to be processed in the brain.

It also sheds light on the molecular mechanisms underlying synaptic plasticity -- the strengthening or weakening of neuronal connections that enables learning and memory. Figuring out this process at the molecular level could increase understanding of how the brain works normally and in diseases where these processes go awry, like Alzheimer's. "We are showing that a structure -- a beautiful structure -- operating at a level of subcellular organization is having a huge effect on the way the entire neuronal system is operating vis-à-vis calcium signaling," Lippincott-Schwartz says. "This is a great example of how, in doing science, if you see a beautiful structure, it can take you into a whole new world."