i An update to this article is included at the end

Trends in Cognitive Sciences

CellPress REVIEWS

Opinion

Cellular Mechanisms of Conscious Processing

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Recent breakthroughs in neurobiology indicate that the time is ripe to understand how cellular-level mechanisms are related to conscious experience. Here, we highlight the biophysical properties of pyramidal cells, which allow them to act as gates that control the evolution of global activation patterns. In conscious states, this cellular mechanism enables complex sustained dynamics within the thalamocortical system, whereas during unconscious states, such signal propagation is prohibited. We suggest that the hallmark of conscious processing is the flexible integration of bottom-up and top-down data streams at the cellular level. This cellular integration mechanism provides the foundation for Dendritic Integration Theory, a novel neurobiological theory of consciousness.

Highlights

Recent breakthroughs in the study of cellular and circuit level aspects of consciousness have led to the conclusion that cortical pyramidal neurons have a central role in the mechanisms of consciousness.

Major theories of cortical processing rely on the separation of forward and backward information flow in the cortex. This separation of information streams is mirrored at the level of single cortical pyramidal cells.

The discovery that general anesthesia separates the two different parts of the cortical pyramidal neurons suggests that there is a way to understand consciousness from the bottom-up (i.e., from cellular mechanisms to cognitive properties of conscious processing).

Given that consciousness has been related to distributed activity patterns in large-scale brain networks, the question emerges as to how exactly single pyramidal neurons can contribute to these macroscale dynamics and, hence, to consciousness.

Global Dynamics and Local Mechanisms of Consciousness

One of the starting points for the science of consciousness was the quest to find the specific neurobiological mechanisms of consciousness [1–4]. Since then, consciousness research has not only become more diverse, but the research focus has also dramatically shifted. There is a growing trend to view consciousness as emerging from interactions between distributed networks of neurons [5–10]. Empirically, this standpoint is supported by a host of studies demonstrating that consciousness is related to global activity patterns of corticocortical and thalamocortical loops. For instance, the state of consciousness can be detected and measured from the activity of large-scale networks [11–13]. This applies to sleep [14], anesthesia [12,13], psychedelic-induced altered states [15], and disorders of consciousness [11–13]. Moreover, several studies have shown that, when the cortex is focally perturbed with transcranial magnetic stimulation (TMS), the extent of cortical activation is dependent on the state and level of consciousness. During consciousness, the perturbation leads to an activation pattern that is complex and engages many cortical areas [16]. However, when the same perturbation is applied during non-rapid eye movement (NREM) sleep [16] or anesthesia [17], the response of the brain is local and fails to engage other brain areas. This measure of the spread of a local perturbation in activity can be successfully used to quantify the level of consciousness [18]. Furthermore, it has been shown that conscious perception is related to 'ignition-like' activity propagation from sensory areas to the frontal regions of the cortex [19,20]. All this evidence fits the intuition that consciousness is related to the activity of large-scale networks, complex processing, and integration (Figure 1A, Key Figure) [5–10].

The success of studying large-scale dynamics of consciousness has overshadowed questions about the cellular mechanisms supporting consciousness. Which processes within single neurons enable communication and interaction between brain areas? Here, we show that studying cellular mechanisms leads to fundamental insights into consciousness and its relationship to global dynamics of the brain (Figure 1B,C). Further experiments specifically targeting these mechanisms constitute one way to make rapid progress in the problem of consciousness.

The Mystery of General Anesthesia

The existence of drugs that can selectively remove consciousness should have been a godsend to investigations into consciousness. The discovery of drugs that block important functional

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components of neural activity have been decisive turning points over the history of neuroscience. For example, tetrodotoxin, which blocks the sodium channels underlying action potentials (APs), enabled groundbreaking research into membrane excitability and synaptic transmission [21]. Yet, despite the knowledge and use of anesthetics since the very beginning of neuroscience itself, there is still no consensus about why they work so effectively and, more importantly, what they tell us about consciousness [22,23]. Part of the mystery lies in what they do not do; namely, they do not completely shut down synaptic transmission or cell firing at concentrations that block consciousness.

Presumably, there is a mechanistic explanation for anesthesia, such that the disparate actions and molecular targets of the different chemicals that lead to loss of consciousness have an unified explanation from cellular function to cognition. If so, it must explain why general anesthesia involves a sudden transition of the conscious state: at a very precise concentration, consciousness is either totally lost or at least disrupted (for a more nuanced view, see [24]). Why? Some theories include the notion of a critical threshold of activation or 'ignition' level of interactions between brain areas [8,10]. The existence of a threshold suggests that some mechanism that is absent under general anesthesia is critical for the integration of long-range information transfer without itself abruptly disrupting cellular properties. However, after nearly two centuries of routine usage of drugs that achieve this, the smoking gun mechanism is yet to be detected.

Here, we propose that the mystery of general anesthesia is pointing not only to an important cellular mechanism that has so far been overlooked, but also to a theory of information segregation and combination that depends on this mechanism. We suggest that anesthesia disrupts some previously unknown local gating mechanism that regulates the propagation of activity patterns in the thalamocortical system (Figure 1B,C).

From the point of view of information flow around the brain, the large **layer 5 pyramidal (L5p) neurons** (see Glossary) have a strategic role because they lie at the nexus of corticocortical and thalamocortical loops [25–28]. Combined optical and **optogenetic** strategies have made it possible to probe and control subcellular compartments in awake and anesthetized animals, which has led to the demonstration that a particular region of **apical dendrite** of L5p neurons serves as a gate or switch, enabling or breaking global brain dynamics [29]. We outline the empirical evidence that this local specific mechanism is, in fact, crucial for consciousness. We suggest that explaining why it is crucial leads to important insights into the nature of consciousness.

The Central Role of Cortical Pyramidal Cells in the Loop of Consciousness

It has been long suspected that cortical L5p cells have a central role in the neurobiological mechanisms of consciousness [2,27,28,30–35] (Figure 2A). The cell bodies of L5p cells lie in layer 5 of the cortex, but their dendrites span across all layers reaching the surface of the cortex in layer 1. Given their location, morphology, and long-range projections within and outside the cortex, the L5p neuron is not only a nexus of information flow in the mammalian brain, but also encapsulates the input/output function of the cortical column. L5p cells are the primary means through which the cortex exerts its control over behavior. What was underappreciated until the advent of careful biophysical studies into its dendritic properties, was that the apical dendrite lent so much to the operation of L5p cells (Box 1). In fact, we would argue that a true understanding of the mammalian brain is impossible without taking into account the biophysical properties of the dendrites of pyramidal neurons [28,36,37].

A full description of the biophysical properties of L5p neurons is a Herculean task because of their intricate shape and complex channel distributions [38,39] and this is constantly evolving as new complexities are discovered [40]. However, at a minimum, to capture the influence of

Glossary

Apical compartment: part of the pyramidal cell toward the surface of the cortex. It integrates contextual information from the corticocortical and thalamocortical loops.
Apical dendrite: a long, tree-like, branched dendrite that arises from the top of the pyramid-shaped cell body of cortical pyramidal cells and has a long trunk oriented straight toward the surface of the cortex. It is particularly prominent in L5p cells.
Basal compartment: part of the pyramidal cell around the cell body including the basal dendrites that controls the spike output of the cell. The basal compartment mainly receives feature specific information.
Burst of APs: a regime of neural activity where the neuron discharges several APs in close succession.
Coupling: a state of the pyramidal neuron in conscious states where the apical compartment can influence the basal compartment.
Coupling compartment: a part in between the apical and basal compartments that mediates interactions between these two parts of the L5p cells.
Dendritic Integration Theory (DIT): theory developed in this opinion article. It proposes that the central operation underlying consciousness is the integration between apical and basal compartments of L5p cells.
Higher order (HO) thalamus: a category of thalamic nuclei that modulate and control cortical processing and that are not involved in relaying information from the sensors to the cortex.
Layer 5 pyramidal (L5p) neurons: large pyramidal cells, the cell bodies of which lie in layer 5, while their dendrites span across all layers reaching the surface of the cortex in layer 1.
Metabotropic receptors: receptors at the cell membrane that do not operate directly as ion channels, but rather activate specific intracellular cascades.
Optogenetics: a set of methods for controlling (or recording) neural activity with light by genetically expressing light-sensitive ion channels in specific neurons.

Key Figure

A Cellular Mechanism Supporting the Global Dynamics of Consciousness

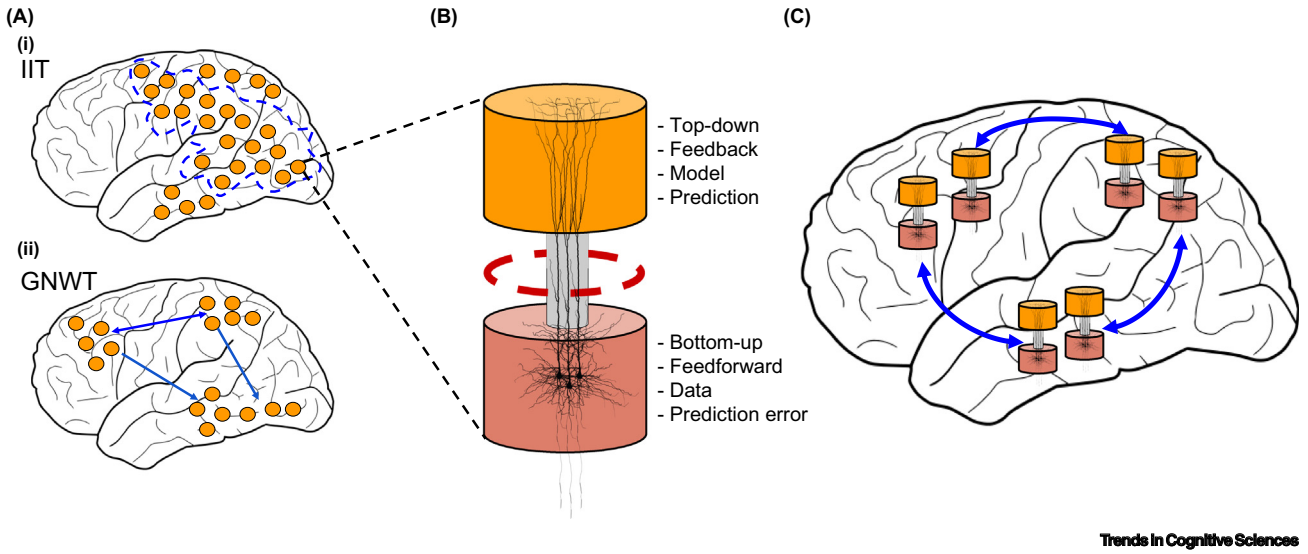

Figure 1. (A) Prominent theories of consciousness, such as the integrated information theory of consciousness (IIT) (i) and global neuronal workspace theory of consciousness (GNWT) (ii) posit that consciousness is associated with reverberating activity in corticocortical networks. In simplified terms, IIT proposes that the interactions within posterior cortical areas underlie consciousness, whereas GNWT sees the frontoparietal network as crucial for conscious access. Presently, the work around these theories is focused on the interactions between distributed networks of neurons. (B) Here, we show that interactions within neurons are also crucial to understand consciousness. Cortical pyramidal cells have two distinct functional compartments facilitating the segregation and recombination of multiple input streams. The ability to flexibly integrate these streams of information is disrupted in unconscious states (broken red ellipse). (C) The central message of the current work is that explanations of consciousness should take these cellular processes into account for gaining insights about mechanisms, placing constraints on theories and proposing decisive experiments.

the three main dendritic arborizations that collect synaptic input, the complexities of L5p cells can be reduced to three compartments (Figure 2A and Box 1 [41]). In this abstraction, the **apical compartment** is a central element that integrates contextual information from the corticocortical and thalamocortical loops [28,36,42]. The **basal compartment** mainly receives feedforward input from specific areas lower in the processing hierarchy [43,44], although it can also receive long-range feedback input [45,46]. The middle compartment, the **coupling compartment**, mediates interactions between the apical and basal compartments [29,41]. The coupling compartment enables flexible combination of the data streams that are anatomically segregated at the apical and basal compartments of L5p cells.

A recent study [29] examined the effect of anesthesia on the **coupling** between the apical and basal compartments by optogenetically stimulating the apical compartment of L5p cells. This conceptually simple maneuver depended on a combination of optogenetic and optical tools allowing the selective stimulation of a subregion of the neurons [47–49]. Therefore, they could measure the effect of this perturbation on activity near the cell bodies of the same cells while varying the conscious state of the animal (Figure 2B). In practice, because of the type of connections that arrive at the apical compartment, this amounts to the question, 'how does the conscious state of the animal affect the influence of contextual information on cell activity?'. However, without optogenetic control of the apical compartment, it would be near impossible to find and precisely control this diverse set of inputs.

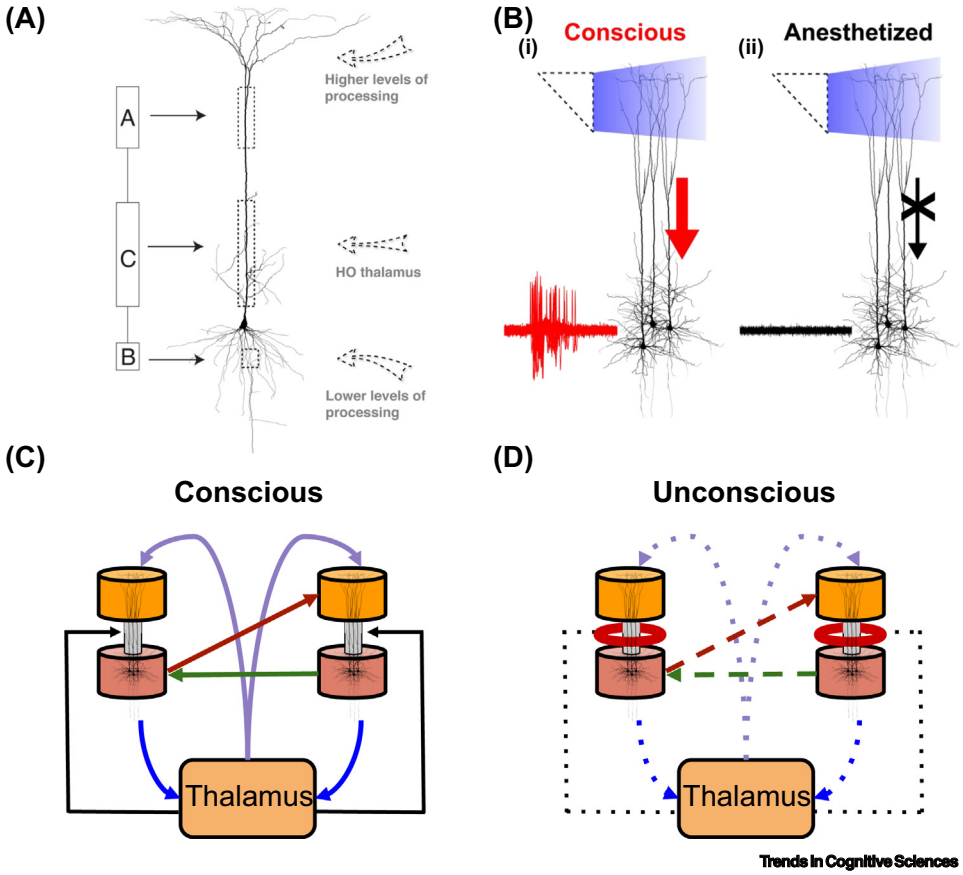

Figure 2. Cortical Pyramidal Cells and their Role in Consciousness. (A) Information processing by the pyramidal cell can be understood as emerging from the interactions between three compartments that correspond to the three main dendritic sub-trees. The apical compartment (A) integrates data from higher stages of processing, whereas the basal compartment (B) mainly receives data from lower levels. The coupling compartment (C) mediates interactions between the apical and basal compartments. Since the axon is attached to the basal compartment, all output from the neuron depends ultimately on information reaching this compartment. (B) In conscious states (i), optogenetic stimulation to the apical compartment (top, blue light delivered via a 'microprism') leads to high-frequency firing of the neurons (bottom, in red). The pyramidal neurons are coupled (as indicated by the bold red arrow). By contrast, under anesthesia (ii), stimulation to the apical compartment has no effect on the activity of the neurons. Therefore, during the unconscious state, all input to the apical compartment is decoupled and cannot influence the neuron (as indicated by the crossed black arrow). (C) From a global perspective, this coupling mechanism gates information flow within the thalamocortical system. In the conscious state, the gate within the cells is open and allows signals to propagate and evolve in the thalamocortical and corticocortical loops. (D) During the unconscious state, cortical pyramidal cells are decoupled (as indicated by the red ellipses), leading to cessation of the activity propagation in the thalamocortical system. Abbreviation: HO, higher order.

The results were remarkable. In the awake state, the stimulation of the apical compartment had a large effect and led to high-frequency firing of neurons (Figure 2Bi). However, anesthetics made this influence disappear: under anesthesia, the same optogenetic stimulation of the apical compartment did not propagate to the soma. In other words, under anesthesia, the basal and the apical compartments were decoupled (Figure 2Bii). These results were replicated across various anesthetics that have different physiological effects and across different cortical areas (frontal, somatosensory, and primary visual cortices), hence making it reasonable to hypothesize that decoupling of the pyramidal neuron is a general property of the unconscious states [29].

Further experiments demonstrated that decoupling happens around the coupling compartment and that decoupling is controlled by the input from **higher order (HO) thalamus**. The authors

Box 1. Pyramidal Cell Primer

Deep pyramidal neurons are cortical output units that encapsulate the combined activity of cortical columns. Different L5p cell populations project to either other cortical or subcortical areas [92]. L5p neurons are distinguished from most other neurons by having a tree-like apical dendrite, which has a long trunk always oriented straight toward the surface of the cortex (Figure I). The thinner dendrites, which collect most of the synaptic inputs, are divided into three subtrees (basal, oblique, and tuft dendrites). Near each of these dendritic subtrees are major spike initiation zones. The basal initiation zone is in the axon that projects from the cell body, generating output APs that signal the next neurons. The apical initiation zone generates long, plateau-like calcium spikes that drive the cell to blast. The coupling zone can boost forward-propagating APs and, therefore, regulates the connection between the apical and basal initiation zones. Clustered (or patterned) synaptic input to thin dendrites causes local NMDA spikes that, similar to the calcium spike, are long, plateau-like potentials; however, they do not propagate actively for any great distance.

The soma of L5p cells communicates with the apical compartments via APs that back-propagate from soma to the apical compartment. In turn, these back-propagating APs lower the threshold for activating the apical compartment, which can generate large calcium spikes that cause burst firing in the soma. This phenomenon, known as 'BAC firing', is thought to be an event that signals a 'match' between feature-specific and contextual information, performing a vital cognitive role subserving intelligent behavior [36,63]. Loss of higher order thalamic input causes this mechanism to break down and correlates with loss of consciousness during anesthesia. In other words, BAC firing is one mechanism of dendritic integration crucial for conscious processing.

How Does Higher Order Thalamus Affect the Coupling Zone?

As yet, the precise details of the effect of the HO thalamus on the coupling zone are unknown. One of the more mysterious facts about the influence of thalamus on cortical function is the unusually large (~50%) fraction of metabotropic versus ionotropic receptor activation [93]. Metabotropic receptor activation can have multiple and diverse downstream consequences, including up- and downregulation of voltage-gated ion channels on excitatory and inhibitory neurons (Figure I). Interestingly, the various biochemical targets of drugs that lead to loss of consciousness are equally diverse and, therefore, this invites speculation about whether the factor that unites both anesthesia and the HO thalamus is their ultimate influence on pyramidal cell compartments. This would still provide multiple options because, apart from the possible direct influences on the pyramidal cell itself, there is also a plethora of possible actions via inhibitory circuitry [94,95], including interneurons with specific dendritic targets and disinhibitory loops (see inset in Figure I).

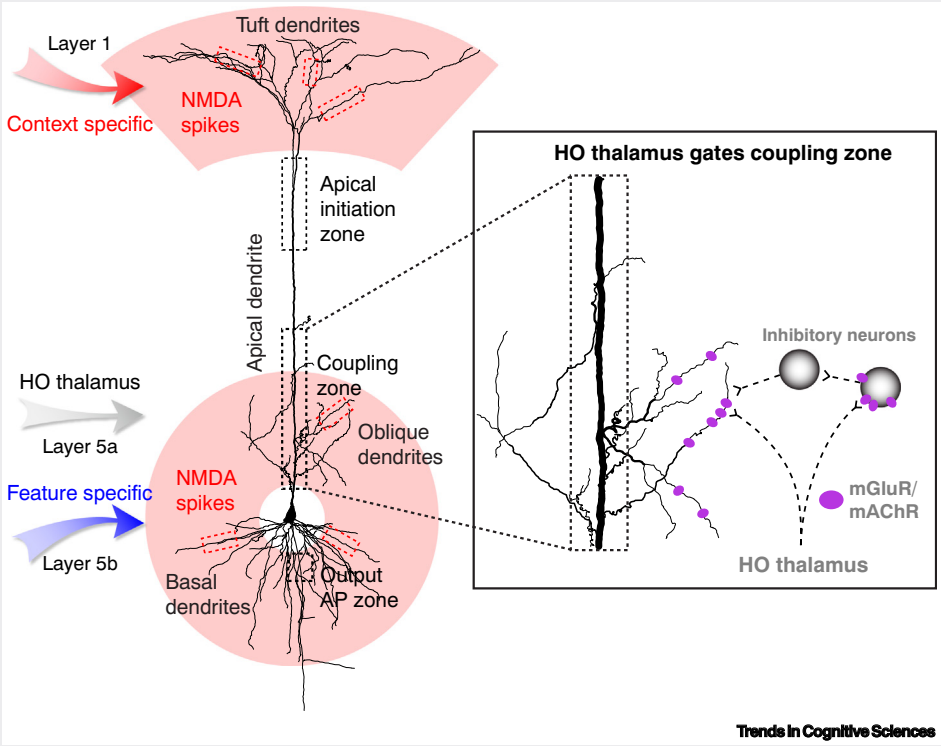

Figure I. Cortical Pyramidal Cells as Multicompartmental Computational Devices. Abbreviations: AP, action potential; HO, higher order; mAChR, muscarinic acetylcholine receptor; mGluR, metabotropic glutamate receptor; NMDA, N-methyl-D-aspartate.

showed that blocking **metabotropic** receptors also decouples the apical and somatic compartments in awake animals. In other words, general anesthesia and downregulation of metabotropic receptor activity at the coupling compartment have the same specific effect. Furthermore, inactivation of the HO thalamus led to a breakdown of the coupling, indicating that the information flow along the cortical L5p cells is controlled by the HO thalamus. HO thalamus is known to activate metabotropic glutamate receptors in all layers of primary sensory cortices [50]. This includes the cortical sublayer (L5a) containing the coupling compartment [51], and thus it appears reasonable to suggest that the control of HO thalamus is mediated via these receptors (Box 1). Therefore, these results could explain why anesthesia leads to loss of consciousness, identifying the coupling compartment of the L5p cells as the crucial switch for consciousness.

These empirical findings [29] are corroborated by several recent findings. First, several laboratories have observed that, during awake conscious states, the activity of the apical compartment of cortical pyramidal cells is strongly correlated to that of the basal compartment [52,53]. Moreover, these works demonstrate that this correlation is not affected by movement or by visual stimulation; hence, the state (conscious versus unconscious) is associated with coupling [29], whereas manipulations within a state (active versus quiet wakefulness or visual stimulation versus darkness) are not [52,53]. Coupling goes hand-in-hand with the state of consciousness.

Second, it has been demonstrated that stimulating the HO thalamus can lead to the awakening of mice [54] and monkeys from anesthesia [55,56] and restore consciousness in patients with disorders of consciousness [57]. In monkeys, this recovery of consciousness was paralleled by increased firing of cortical deep layer (including L5p) neurons and an enhancement of the efficacy of corticocortical and thalamocortical communication and coherence [55]. Jointly, these results demonstrate that cortical pyramidal neurons, the coupling compartment within them, and the HO thalamus have a central role in the neurobiological mechanisms of consciousness. Lastly, the tight control of signaling along the apical dendrite of L5p neurons by neuromodulation has been demonstrated under *in vitro* conditions [58,59].

The Dendritic Integration Theory

From a Local Switch to a Global Reverberation

Most theories of consciousness agree that reverberating activity in thalamocortical loops is essential for consciousness [10,60,61]. However, it was not known previously that the pyramidal neuron could serve as the fulcrum, allowing these loops to work synergistically and that this synergy is controlled by a highly specific cellular mechanism. Recent data [29] show a tight regulation of the coupling across the apical dendrite, suggesting that these neurons serve as a local gating mechanism controlling the interaction between corticocortical and thalamocortical loops. This mechanism leads to a theory, **'Dendritic Integration Theory' (DIT)**, for explaining why global dynamics of large-scale networks are different between conscious and unconscious states and why local perturbations lead to different effects depending on the state of consciousness (Table 1). If the pyramidal cells are in the coupled state, activity can freely propagate, activate HO thalamus, spread through corticocortical loops, and give rise to global dynamics of consciousness (Figure 2C); this cannot happen if the activity propagation is blocked by shutting the local gate in L5p cells. Decoupling single pyramidal neurons decouples the loops and, hence, switches off the reverberating nature of conscious processing (Figure 2D).

DIT is compatible with the leading theories of consciousness and provides neurobiological grounding for their main claims (Table 1). For instance, according to the integrated information theory of consciousness (IIT [8,9,62]) consciousness corresponds to the neuronal processing

Table 1. How Dendritic Integration Theory Explains Global Dynamics

Phenomenon	Description	Proposed explanation
Conscious state is related to sustained complex neural dynamics	Macroscopic measures of neural activity [e.g., fMRI, electroencephalogram (EEG)] show that consciousness is related to global activity patterns that reflect integration and coordination [11–13]	Coupling of pyramidal cells allows activity to be coordinated and integrated in thalamocortical loops. Such global coordination cannot happen if pyramidal cells are decoupled
Consciousness is related to signal propagation in thalamocortical networks	Combining EEG and TMS shows that local perturbation leads to complex activity patterns in consciousness and focal response in unconscious states [16–18]	Pyramidal neurons are only coupled in conscious state; therefore, local perturbation can only grow and propagate in thalamocortical loops in conscious state
Conscious perception is correlated to a late 'ignition' of large-scale networks	Consciously perceived stimuli diverge from unperceived stimuli only around 200–300 ms when diverse regions of brain are activated; unconscious stimuli can activate cortex locally [19,20]	Unconscious stimuli can activate basal compartments of pyramidal neurons. Given time, the apical compartment is recruited, maintained by, and incorporated into thalamocortical processing loop leading to consciousness; for this, L5p cells must be coupled
Consciousness is related to activation of 'hub' regions of cortex	Hub regions, such as prefrontal and parietal regions, are often activated in tasks involving conscious perception [7,10]	L5p cells in cortical regions that are more densely anatomically coupled to either the HO thalamus or other cortical areas are more easily coupled and recruited into thalamocortical loop
Conscious state is characterized by specific temporal dynamics	Under anesthesia, L5p neurons are key drivers of slow oscillations [91]; in conscious state, infragranual (including L5p) neurons generate alpha-beta rhythms associated with consciousness [55]	L5p basal compartments decoupled from apical compartment participate in generation of slow oscillations; in coupled state, the intrinsic properties of the L5p neurons drive higher frequencies

complex that has maximally irreducible cause–effect power on itself [8,9,62]. Shutting the gates at the coupling compartment would lead to a drastic breakdown in the cause–effect repertoire and consciousness would fade [8,9,62]. Hence, DIT provides a specific cellular mechanism for controlling information integration in the thalamocortical system.

Dendritic Integration of Data Streams

We have argued that large-scale dynamics are the result of cellular interactions and, therefore, that it is crucial to find a consistent through-line explanation from the level of cells and circuits up to consciousness. More than that, we contend that the biophysical mechanisms within the pyramidal neurons do conceptual work in terms of understanding consciousness. Our second main thesis is that dendritic integration in L5p cells happening in a massively parallel fashion across the cortical sheet can explain properties of conscious experience.

From the biological facts, we take for granted that increasing the complexity of individual neurons and their relationship to connectivity allows the brain to conditionally separate and recombine information streams even at the cellular level [36] (Box 1). Conceptually, this means that categorically different classes of information can be kept separate and ultimately brought together in a complex operation determined by the coupling properties of L5p cells. If the L5p cells are coupled as in the conscious state, simultaneous input to the apical and basal compartments leads to a **burst of APs** [36,63]. In essence, bursts could signal to the rest of the brain that a match between the data streams has been found regarding the particular sensory or cognitive feature that is represented by the particular cortical column. Next, we consider the identity of these data streams from the computational and cognitive perspective.

Computational Theories of Integrating Data Streams

The mechanism of flexibly combining segregated information streams could provide the cellular foundation for computational theories of brain functioning that depend on the integration of bottom-up and top-down information streams. One of the early theories of this kind is the adaptive resonance theory [64], which has also been applied to consciousness [65]. Presently, the most prominent computational frameworks that depend on a dual-stream information flow are based on the principle of free energy minimization [66]. These computational theories are predictive coding (PC), which has various implementations [67–69], and active inference [70,71].

According to the most prominent implementations of PC [67,68], predictions sent from higher to lower levels of processing try to explain away activity propagating from lower to higher levels by suppressing the sensory signals that match the predictions. What cannot be predicted is passed on to higher levels as prediction errors.

DIT is in principle compatible with the idea that the two information streams impinging on L5p neurons are predictions and prediction errors. Although the biophysical processes intrinsic to the L5p cells prescribe them to amplify the match between the two streams [36,63], this match could be turned into a suppression via an appropriately connected inhibitory connection. While there is flexibility as to which computation is implemented, any theory that tries to explain how the brain works should try to accommodate the fact that intrinsically the L5p cells compute the match between top-down and bottom-up information streams. This is an important constraint from neurobiology, because L5p neurons are the key output of the cerebral cortex and broadcast the outcome of dendritic integration to diverse regions of the brain [72].

Which Cognitive Streams Are Integrated?

One of the most exciting outcomes of the past decade of consciousness research has been the description of the pervasive effect of prior knowledge and predictions on conscious perception [73]. For example, valid expectations facilitate access to consciousness [74,75]. Similarly, having an expectation about a stimulus can make the participants consciously experience the stimulus even if none is objectively presented [76,77]. Furthermore, it has been proposed that during dreams conscious experience is generated partly by the top-down stream [78,79].

Theories of consciousness need to offer a natural way for explaining why conscious experience is determined by the synergy between top-down and bottom-up information flow. Recent ideas that are based on the free energy principle are appealing exactly because of this reason [80–82]. DIT is compatible with these views and offers a specific neurobiological mechanism of this synergy.

According to DIT, each cortical column is signaling to the rest of the brain whether the sensory or cognitive feature represented in that column is present (in the real or imagined world). The basal compartment integrates feature-specific information, whereas the apical compartment receives internal variables that relate to, or could be associated with, the feature. The internal variables could be context and expectations, but they could also be semantic knowledge or episodic memory about the feature. Attention, working memory, or task-set involving the feature could all be seen as the internal stream targeting the apical compartment. Those features that match the internal variables are amplified through the dendritic integration process [36,42]. If the feature does not match the internal processes, the feature will not make it into consciousness because, despite the basal activation, there is no apical activation and no dendritic integration (e.g., inattentional blindness where, for example, if one is counting basketball passes, one might not notice salient objects such as the human in a gorilla costume [83]). According to DIT, processing that involves the basal compartment without being coupled to the apical

compartment, is nonconscious. By contrast, it has recently been suggested that under certain circumstances strong activation of the apical compartments might be able to generate conscious experiences like dreaming [79].

These two information streams could also be seen as the first-order representation in the basal compartment and the higher order representation in the apical compartment. Hence, this cellular mechanism within the L5p cells could also lay the foundation for higher order theories of consciousness [84–86]. From this perspective, the higher order aspect of processing is not related to specific areas (e.g., the prefrontal cortex), but rather to a specific data stream targeting the apical compartments of pyramidal cells. This data stream might partly originate in the prefrontal cortex, but its relevance to cognition and consciousness is to be found on the level of those L5p cells that receive projections from it.

In summary, the architecture and biophysical properties of the L5p cells enable flexible integration of segregated data streams. The precise labeling of the classes of information that are in fact separated and combined by this mechanism is, of course, crucial in the long run to truly understand the essence of the operation being performed. However, here we point out that the segregation and integration of data streams within a pyramidal neuron are conceptually fundamental and render cognitive, high-level, or global descriptions contingent on the implications of the biophysics. Dendritic integration of segregated data streams might be the defining characteristic of conscious processing.

Dendritic Integration in Conscious Processing

Further evidence for DIT in conscious processing comes from another recent experiment [87]. These authors conducted a sensory detection task with mice where stimuli were presented sometimes below, sometimes above, and sometimes at the threshold for perceptual report. This approach was inspired by seminal work in humans [19] and rodents [88,89]. The authors focused on the sensory cortical area involved in processing this particular whisker stimulus and observed that both the spiking activity of L5p cells and an explosive event in their apical compartments [63] were well correlated with the behavior of the animal. Most importantly, directly

Box 2. Dendritic Integration and HO Thalamus in Conscious Processing

One question left unanswered so far concerns the exact role of HO thalamus in dendritic integration and consciousness. It has been suggested that HO thalamus is the central orchestrator of activity propagation in thalamocortical networks [26,96]. Accordingly, there is a line of reasoning suggesting that HO thalamus is directly relevant for understanding consciousness [25–28]. However, according to a currently more dominant view, HO thalamus simply supports or enables the cortical interactions that underlie consciousness [4,61,97].

Based on [29], one could think that this latter view is on the right track: perhaps the only role of HO thalamus is to allow the L5p cells to be coupled. However, a recent extension to the study that looked at the influence of dendritic activity on conscious perception [87] revealed that this simple view does not capture the full complexity of the interaction between dendritic integration in L5p cells and processes in HO thalamus. In [98], the authors asked what downstream targets of the L5p neurons are relevant to conscious perception. They used a chemogenetic approach to selectively block the projections from somatosensory cortex to particular subcortical targets. Here, they were able to establish that, above all, the influence of L5p neurons on HO thalamus was crucial for the perceptual report of the animal.

Thus, it appears that HO thalamus controls coupling within the L5p neurons [29] and, conversely, the L5p neurons convey information to the HO thalamus [98]. The details of these interactions between HO thalamus and L5p cells are not completely worked out yet, but anatomical and physiological evidence shows that specific excitatory recurrent loops are formed between L5p neurons of a particular cortical column and the corresponding neurons of HO thalamus [99,100]. According to DIT, these recurrent cortico-thalamo-cortical loops can maintain the contents in consciousness for as long as needed and, hence, contribute to computations that require working memory. Furthermore, this research demonstrates why the state and contents of consciousness are intertwined [27,28]: contents are represented by the specific subset of L5p neurons coding for the particular feature and projecting to HO thalamus [98], but these L5p neurons contribute to conscious experience only when their compartments are coupled, which is a property controlled by HO thalamus [29].

modulating the apical compartments through pharmacological intervention or optogenetics greatly affected the detection behavior of the animal [87]. The fact that the causal manipulation of the apical compartments led to changes in behavior suggests that dendritic integration of data streams within L5p cells is crucial for experiencing specific contents of consciousness. A follow-up study suggested that perception relies especially on those L5p cells that project to HO thalamus (Box 2).

If sensory input enters corticothalamo-cortical loops in the conscious state, it can be amplified through dendritic integration and is able to influence and engage distributed networks. Through this mechanism, DIT can explain phenomena such as ignition-like dynamics associated with consciously perceived stimuli (Table 1). Therefore, DIT is compatible with the global neuronal workspace theory of consciousness (GNWT, [6,7,10,90]). GNWT proposes that the cortical frontoparietal network broadcasts information to other brain areas and that such global access is the essence of conscious processing. Attentional amplification and global broadcasting through recurrent connections are impotent if the pyramidal cells are decoupled. Only if the streams of processing are integrated within single L5p neurons can ignition-like dynamics be generated globally.

Concluding Remarks

Consciousness is a problem that has to be approached from many angles. Here, we have advocated for a neurobiological research program toward understanding consciousness. We have made two main claims: first, consciousness relies on the dendritic integration of two anatomically and functionally segregated data streams; and second, global dynamics of the conscious brain are gated by specific cellular mechanisms. The advantage of approaching consciousness from neurobiology is that these claims can be tested here and now by the tools available to modern neuroscience (see Outstanding Questions). Perhaps now due to the unprecedented advances in the techniques to dissect the neural circuits in the conscious or unconscious brain, the time is really ripe (*cf* [1]) for figuring out the neural basis of consciousness.

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Outstanding Questions

Does artificial decoupling of pyramidal neurons, for instance by blocking metabotropic glutamate receptors, lead to loss of consciousness? Is decoupling the elusive explanation for anesthesia?

Is decoupling of L5p neurons also observed when consciousness fades during deep sleep? What about other unconscious states, such as traumatic brain injury or coma?

Are the pyramidal neurons coupled in REM sleep? At least in humans, this state is associated with conscious experiences in the form of dreams.

Would artificial coupling during the unconscious state lead to behavioral and neural indices of consciousness? One direct way of testing this would be to stimulate the HO thalamus optogenetically while assessing the coupling of the L5p neurons. How many L5p neurons need to be coupled for a global state change?

Are there other structures beyond the HO thalamus that can control and change the coupling of the L5p neurons? It might be that there are cortical long-range projections that can target the coupling compartment and, hence, are able to control the coupling. There could also be hub areas: as soon as a substantial number of L5p in such an area are coupled, the coupling propagates rapidly and the global brain state shifts.

How selective is the control of the coupling compartment? Is coupling homogenous throughout the cortex? Or can coupling be controlled in a more local fashion? If the latter were true then the control of coupling could turn out to be a key mechanism of selective attention.

Can coupling be measured noninvasively? Can coupling be manipulated noninvasively (e.g., by TMS)? What is the neural signature of coupling in humans?

Does conscious perception always rely on the integration of top-down and bottom-up data streams? Phenomena like hallucinations, dreams, and mental imagery seem to suggest that under certain circumstances the top-down stream can dominate perception.

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Update

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Correction

Cellular Mechanisms of Conscious Processing

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Due to an error, the last line of the abstract referred to “Dendritic Information Theory” rather than “Dendritic Integration Theory”. This has been corrected online such that the last line of the abstract is now: “This cellular integration mechanism provides the foundation for Dendritic Integration Theory, a novel neurobiological theory of consciousness”. The authors apologize to readers for any inconvenience.