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Trends in Cognitive Sciences

Opinion

Cellular psychology: relating cognition to context-sensitive pyramidal cells

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'Cellular psychology' is a new field of inquiry that studies dendritic mechanisms for adapting mental events to the current context, thus increasing their coherence, flexibility, effectiveness, and comprehensibility. Apical dendrites of neocortical pyramidal cells have a crucial role in cognition – those dendrites receive input from diverse sources, including feedback, and can amplify the cell's feedforward transmission if relevant in that context. Specialized subsets of inhibitory interneurons regulate this cooperative context-sensitive processing by increasing or decreasing amplification. Apical input has different effects on cellular output depending on whether we are awake, deeply asleep, or dreaming. Furthermore, wakeful thought and imagery may depend on apical input. High-resolution neuroimaging in humans supports and complements evidence on these cellular mechanisms from other mammals.

Highlights

Cognitive abilities and disabilities are related to cooperative context-sensitive cellular mechanisms.

We review research in cellular psychology with a focus on contextual disambiguation in perception, selective attention, working memory, and predictive processing.

These cellular mechanisms operate differently in different states of mind from deep sleep to wakefulness.

They increase prediction success via feedforward and recurrent transmission of inferences.

Layer-specific neuroimaging in visual occlusion and other paradigms in humans provides complementary evidence that supports inferences drawn from cellular physiology.

Cognitive capabilities that depend on context-sensitive dendrites

Context-sensitive apical dendrites (see Glossary) of neocortical pyramidal cells have been implicated in cognition [1–11] and its disorders [12–15]. This context-sensitive style of computation is cooperative, in that it tends to increase agreements and reduce conflicts between mental events, and it provides cellular foundations for mental life, shedding light on the brain's evolution, development, and pathologies [16]. We review research implicating these dendritic mechanisms in well-specified cognitive capabilities. These studies of dendritic computation suggest that we are moving beyond the leaky integrate-and-fire **point neuron** assumption that dominated much of 20th-century systems and cognitive neuroscience.

According to that point neuron assumption synapses are functionally equivalent, varying only in the strength of their excitatory or inhibitory effects. Although this may be an adequate way to think of many neurons, refined studies of dendritic computation in neocortical pyramidal cells now show that in many of them, their **apical tuft dendrites** in layer 1 have modes of operation distinct from their **basal dendrites**. Specifically, tuft inputs are combined at a second point of integration located near the top of the apical trunk. These apical inputs come from diverse sources of internally stored information within and beyond the neocortex [17]. In one common mode of operation, transmission of information about the feedforward input to basal/perisomatic synapses is amplified when relevant to the broad context of activity elsewhere, as signaled by the apical input. This mode of operation is referred to as '**apical amplification**' (AA). It occurs when feedforward and contextual inputs both tend to activate the cell, so, that is what we call 'prediction success'. AA is distinguished from modes of operation in which the apical input can generate output by itself. These modes are referred to as '**apical drive**', which can be seen as a kind of 'self-fulfilling prophecy'.

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Although the functional distinction between apical and basal dendrites was reported more than 20 years ago [18], its relevance to cognition only began to gain widespread attention within cognitive science when explicitly related to conscious experience [6,19]. Other studies have explored the role that context-sensitive cells have in many cognitive capabilities, including studies of conscious experience, contextual disambiguation in perception, selective attention, working memory (WM) and imagery, emotional prioritization, cognitive control, and learning [16]. We review these advances and show how the flexible dynamic adaptation of cognition to current circumstances depends upon context-sensitive cellular mechanisms. Our focus here is on perceptual disambiguation and selective attention. The coherence of these findings suggests that they are paving the way for a new field of research that can significantly advance our understanding of mental life in sickness and in health. This field of research is further encouraged by advances within artificial intelligence and machine learning that are inspired by the evidence for cooperative context-sensitivity in mammalian neocortex [20–23].

We build on a theoretical framework that distinguishes between two subsets of synaptic input: **receptive fields** and **contextual fields** [24–30]. These concepts have been further developed by computational models that distinguish different modes of apical operation. This includes closely related models showing that the segregation of inputs into feedforward and contextual subsets can support object recognition, contextual disambiguation, flexible retrieval of learned sequences, and an overall form of management that is much the same as 'cognitive control' [31,32]. Though much evidence of these mechanisms comes from non-human cellular physiology, it is complemented by various paradigms in awake humans using high-resolution neuroimaging [3]. Overall, this research field is growing so rapidly (Box 1) that our review must be highly selective. By analogy to 'molecular biology', and encouraged by evidence relating cognition to genetics and cooperative networks of neurons [33], we call this new field '**cellular psychology**'.

As we focus on cellular processes, readers may assume that our approach is reductionist. On the contrary, we see it as consonant with non-reductive supervenience. Supervenience implies that

Box 1. The cooperative context-sensitive style of neuronal computation

Neocortical capabilities arise from interactions between multiple streams of concurrent feedforward processing within and between regions. Cooperative interactions tend to maximize agreement and minimize disagreement. Feedforward and contextual inputs agree when they both tend to activate the cell, a condition known within cellular neurophysiology as 'coincidence detection'. A subset of inputs to a local microcircuit operates as a context when it modulates transmission of information about other inputs, rather than about itself [29]. Concrete examples of cooperative context-sensitive computation have been given by relating it to symbol and sentence interpretation when reading [15]. One example of cellular activities that disagree are those implied by approach-avoidance conflicts. Another is that implied by the alternatives between which normalizing competition chooses [117]. This style of computation resonates with: 'cells' inferred on psychophysical grounds to unify our understanding of normalization, selective attention, and WM [117]; Festinger's theory of cognitive dissonance reduction and theories of predictive coding [118]; the theory of constrained rationality [119]; and neuroconstructive views of cognitive development [77,120–122]. It is relevant to conceptions of signal-to-noise ratio because what is 'signal' depends on context. Furthermore, our emphasis on context-sensitive cellular mechanisms resonates strongly with ample evidence that the capabilities and evolutionary enhancements of intracellular processes have long been underestimated within psychology and systems neuroscience [123].

Formal quantification of 'contextual-modulation' is discussed in the section 'Cooperative context-sensitive pyramidal cells'. Informally, it can be thought of as selective amplification/attenuation of feedforward transmission without becoming part of the information transmitted. Consider interactions between musicians in an orchestra. The score specifies their distinct contributions, and they coordinate their actions by attending to each other and the conductor, who operates at a higher level of abstraction. Similarly, but in vastly greater numbers, context-sensitive pyramidal cells make their own specialized contributions and coordinate their activities by receiving information about the context of concurrent activity elsewhere. The context of other streams and higher levels of abstraction to which any given cell listens varies greatly across cells. Cellular outputs are more sensitive to concurrent processing in streams of processing that are in some sense 'nearby' in space, and time, and to higher levels of abstraction in the same stream of processing.

nothing happens in your mind without corresponding events happening in your brain, whereas plenty happens in your brain without any corresponding event happening in your mind. As we see it, mental events correspond to macroscopic patterns of microscopic activity that are to some extent coordinated by cooperative context-sensitive interactions between the hosts of local cortical microprocessors. So, the coherence and effectiveness of percepts, thoughts, and actions depends on that coordination – which changes the activities being coordinated.

Cooperative context-sensitive pyramidal cells

Basal and apical dendritic trees are distinct in the morphology of many neocortical pyramidal cells and receive inputs from different sources (Figure 1). Basal input comes predominantly from locally specific subsets of cells in lower hierarchical levels. Input to the apical tree in layer 1, aka the tuft, comes from diverse sources, including lateral connections within regions, feedback or top-down connections from higher regions, higher-order thalamus, and the amygdala [17]. Much evidence suggests that these two subsets of input are regulated by three distinct sets of **inhibitory interneurons (IINs)** (Figure 1A). One inhibits basal input, one inhibits apical input, and one

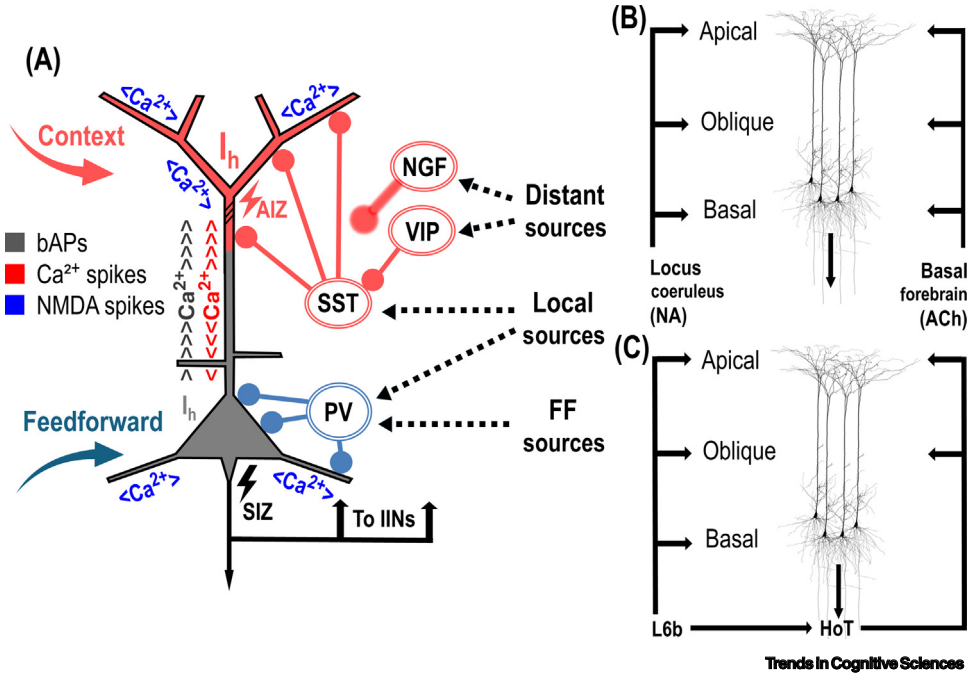

Figure 1. Context-sensitive pyramidal cells together with their main local microcircuitry and systemic connections. (A) This diagram of a context-sensitive pyramidal cell shows three ways in which activation flows within those cells: short-range bidirectional (**<Ca $^{2+}$>**); long-range bidirectional (**<<<<Ca^{2+}>>>>**); and long-range unidirectional (>>>>**Ca^{2+}>>>>**). In the modulatory mode of operation, input from diverse sources amplifies transmission of information from the cell's receptive field (i.e., the set of feedforward inputs to which the cell is selectively sensitive). Ih denotes the hyperpolarization activated current flow through HCN ion channels (printed larger in apical dendrites because that is where they are most dense). IINs are four classes of inhibitory interneurons that are primarily distinguished by their distinct intracellular molecular markers [i.e., PV, SST (aka SOM), VIP, and NGF cells). VIP cells predominantly disinhibit apical dendrites. The output of NGF cells is shown in a highlighted form and without a well-specified target because they inhibit nearby cells via volume release of GABA, mainly in the upper layers, but also to a lesser extent in deeper layers. Slightly modified from [37]. (B,C) Diagrammatic representations of neuromodulatory input to cells within a local cortical column, exemplified here by layer 5b cells. (B) Sources of cholinergic (ACh) and noradrenergic (NA) neuromodulators and the intracellular locations of their neocortical projections. (C) Connectivity of layer 6b cells (inputs to L6b not shown). Targets of the cell's outputs other than those to HoT are not shown. Abbreviations: AIZ, apical integration zone; FF, feedforward; HoT, higher-order thalamus; IIN, inhibitory interneuron; SIZ, **somatic integration zone.**

Glossary

Amplifying context: input to a neocortical pyramidal cell that strengthens transmission of information about other inputs while transmitting little or no information specifically about itself.
Apical amplification (AA): a mode of operation in which input to apical dendrites in layer 1 amplifies transmission of information about basal/perisomatic input.
Apical drive: a mode of operation in which input to apical dendrites in layer 1 generates axonal spiking output by itself.
Apical integration zone (AIZ): a zone near the top of the apical trunk that integrates the inputs to dendrites of the tuft and signals to the soma when that exceeds a threshold that is briefly lowered by an axonal action potential. It transmits excitatory but not inhibitory signals to the soma.
Apical isolation: a mode of operation in which input to apical dendrites in layer 1 has no effect on the cell's current output – though it may alter some synaptic strengths.
Apical tuft dendrites: the subset of pyramidal cell dendrites separated from the soma, or 'cell body', by the apical trunk.
Basal dendrites: those that feed directly into the soma, from where the axonal action potentials are generated.
Cellular psychology: a young field of research in which cognitive capabilities are related to cellular capabilities that exceed those of leaky integrate-and-fire point neurons.
Context-sensitive apical dendrites: context-sensitive apical dendrites of neocortical pyramidal cells have a distinct set of inputs that usually operate as a context that amplifies its feedforward information transmission.
Contextual field input: inputs to a cell from internal sources that can amplify the cell's response to its receptive field input.
Cooperative interactions: interactions between cells or microcircuits that tend to maximize agreement between their activities and minimize disagreement.
Inhibitory interneurons (IINs): cells that send inhibitory signals to specific locations on nearby cells; PV IINs target basal and perisomatic locations; SST IINs target tuft locations; VIP IINs are disinhibitory and preferentially inhibit SST cells.
Modulate: amplify or attenuate.

disinhibits apical input by suppressing its inhibition [34–37]. Disinhibition of basal input by long-range input is either absent or far less prominent than long-range disinhibition of apical input [38].

Layer 5 pyramidal cells are the best-known examples of those with two sites of input integration [6]. The extent of the set of context-sensitive pyramidal cells is unknown, primarily because the multisite patch-clamping experiments by which the effects of apical activation can be directly studied are of exceptional technical difficulty. Nevertheless, pyramidal cell capabilities presumably depend on many variables, such as species, age, region, and apical trunk-length [39]. There are grounds for supposing that some layer 2/3 cells in humans may also have a functionally distinct point of apical integration [40], so that is a major issue for the future.

In rat visual cortex the ability of apical input to operate as an amplifier requires trunk-length to be about half a millimeter or more [39]. Cortical thickness and pyramidal cell trunk lengths tend to be greater in primates, especially in humans, so the distinctive functions of apical input may be even more important for them. We focus on evidence from rodents not because we suppose that all mammals have the same cellular capabilities but because our review provides grounds for supposing that pyramidal cells with context-sensitivity are a conserved feature throughout mammalian evolution. They have a crucial role in perception and learning both during infancy [35] and when mature [41–43]. Their evolutionary enhancements may provide crucial insights into cross-species differences in cognitive capabilities, as suggested by the finding of distinctive rose-hip interneurons in the superficial layers of human neocortex [44], and perhaps including cellular bases for uniquely human scientific, creative, and ethical capabilities.

When operating as an amplifier, apical input that would have no effect by itself greatly increases the cell's response to coincident activation of the cell by the pattern of basal inputs to which it is selectively sensitive [18,45–47]. As shown later, this amplifying mode of apical operation probably provides cellular bases for various cognitive capabilities, with its implications for perception currently being the most explored.

AA has been quantified using partial information decomposition. Input to a neocortical pyramidal cell or to the microcircuit in which it is embedded operates as an **amplifying context** if it is highly specific in space and time and strengthens transmission of information about other inputs while transmitting little or no information specifically about itself [29]. Dendrite-specific current injections in rodent L5 cells [27] and multicompartmental cellular modeling [48] confirm that inputs to distal apical dendrites can operate as a contextual amplifier that generates bursts of axonal spikes by triggering calcium spikes that travel down the apical trunk [10]. The high spatio-temporal specificity of its amplifying effects distinguishes them from those of the classical neuromodulators. The recent advances in information theory used to quantify these discoveries are not widely known, so a highly simplified introduction to those mathematical advances is provided in Chapter 8 of *The Cooperative Neuron* [16].

Our focus on cooperative context-sensitivity adds to previous conceptions of dendritic computation in basic ways. It assumes two functionally distinct points of input integration, thus implying that many pyramidal cells operate as **two-point neurons**. Anatomically, that is motivated by the clear separation of the apical tuft and its inputs from basal and perisomatic dendrites. Physiologically, it is motivated by findings showing that neocortical pyramidal cells have either one or two points of input integration [27,39,48]. Formally, it is motivated by the huge interpretative load arising if distinct contributions to output of more than two inputs are to be distinguished by cells to which they project. Given two sets of input, there are only six information theoretic components to be considered per cell, but for three it is 20, and for four it is 168 [49]. Cooperative

Point neurons: neurons that integrate all their synaptic inputs, either linearly or non-linearly, and signal the extent to which that net sum exceeds a threshold; as in leaky integrate-and-fire cells.
Receptive field input: feedforward input that specifies a cell's selective sensitivity.
Somatic integration zone (SIZ): a zone in the soma that receives input directly from basal and perisomatic synapses and indirectly from the apical tuft and initiates sodium axonal action potentials (i.e., spikes), when that input exceeds a threshold.
Two-point neurons: neurons that have two functionally distinct subsets of synaptic input, usually with one subset modulating transmission of information about the other subset.

context-sensitivity emphasizes excitatory voltage-dependent sodium and calcium ionic currents by which the two input-integration zones communicate [45,48]. It offers a new perspective on the relations between prediction success maximization and prediction error minimization [37].

Regulation of cellular function in various states of mind

Context-sensitive pyramidal cells are crucial to the regulation of mental state as well as to the specification of experienced content [10,50]. Three states have long been distinguished on psychological and neurobiological grounds: the typical wakeful state with moderate levels of cholinergic and adrenergic activation; slow wave sleep with low to minimal levels of cholinergic and adrenergic activation; and dreaming during rapid eye movement (REM) sleep with high cholinergic and minimal adrenergic activation [32,51]. There may also be a wakeful state in which fictive percepts and actions occur and during which there are high levels of both cholinergic and adrenergic activation. Images and thoughts may therefore involve a particular type of this fourth state, which we refer to as a form of apical drive. Indeed, multicompartmental modelling of layer 5 pyramidal cells indicates at least four distinct modes of apical operation similar to the states of **apical isolation**, AA, and two types of apical drive [31,32,48].

States of wakefulness, vigilance, and sleep depend on cholinergic and noradrenergic subcortical nuclei whose axons have terminals in layer 1, where context-sensitive apical dendrites of pyramidal cells lie [52]. Thus, regulation of mental state by those neuromodulators depends in part on their actions at the apical dendrites of neocortical pyramidal cells [53,54].

Cholinergic, noradrenergic, and other neuromodulators operate with low temporal and spatial resolution, but selective attention can operate with high local specificity, so additional circuits for rapid and more focused effects must be considered. Neurons in neocortical layer 6b (L6b) have properties that could serve that function [55]. They seem tuned for highly specific regulation of thalamocortical activity because their projections to layer 5 and higher-order thalamus have high spatial specificity. L6b cells activate fast, ionotropic, glutamatergic synapses that maintain or increase their excitatory thalamocortical effects when their activity is sustained. These activities are ideal for maintained, narrowly focused, attention. Indeed, optogenetic stimulation of L6b cells rapidly generates high-frequency gamma oscillations associated with attention and confirms previous observations of apical calcium spiking without backpropagation initiation [55]. Furthermore, L6b neurons are driven by inputs from higher-order cortex [56] and from neuromodulators involved in wakefulness, attention, and WM such as noradrenaline, acetylcholine, and orexin [57].

As they are directly linked to the thalamocortical system, L6b cells could have roles in cognition beyond focusing attention and the temporary maintenance of activity. During REM dreaming, frontal and other higher-order cortical activity is low [58], but cholinergic activation is even higher than during wakefulness. In that state, L6b activity would be unconstrained by higher-order cortex leading to relatively unconstrained and potentially incoherent thalamocortical activities sparking eclectic experiences reminiscent of dreams [51]. Table 1 relates neuromodulation and cognitive capabilities to each of these four putative modes of apical operation.

L6b cells target NMDA receptors in the tuft of L5 cells (Figure 1C), so, they are potential causes of powerful dendritic spikes at the apical integration site. Therefore, in addition to a role in dreaming, L6b and apical dendrites could have key roles in context-sensitive perception and higher forms of cortico-thalamic interaction [59]. They may also contribute to wakeful thoughts.

Layer 6b cells are also likely to have a role in WM because they tend to maintain activity of pyramidal cells in the higher cortical layers. That issue is complex, not least because WM is a family of

Table 1. Four putative modes of apical operation[a,b]

Neuromodulation & abilities enabled	Apical amplification	Apical isolation in SW sleep	Apical drive in REM sleep	Apical drive in awake thought
Cholinergic	Mod – High	Low – minimal	Maximal	High – maximal
Noradrenergic	Mod – High	Low – minimal	Minimal	High – maximal
Orexinergic	Mod – High	Low – minimal	Minimal?	High – maximal
Conscious experience	Yes	No	In part Yes In part No[c]	Yes
Cognitive abilities enabled[d]	All except imagery and thought?	Consol./re-org. of LTM?	Consol./re-org. of LTM? Emotional priority?	All except high-level perceptual processing?

[a]For reviews of evidence on which this table is based see [16,32,54].
[b]Abbreviations: Consol, consolidation; LTM, long-term memory; Mod, moderate; REM, rapid eye movement; Re-org, re-organization; SW, slow wave.
[c]See Table 4.1. of [16] for eight ways in which the dream state is like wakefulness and eight ways in which it is like SW sleep.
[d]Cognitive capabilities considered were contextual disambiguation in perception, selective attention, working memory, cognitive control, emotional prioritization, learning, and long-term memory.

phenomena, not a single process [60]. Nevertheless, though much remains to be clarified concerning dendritic function and WM, there is much evidence that special capabilities of apical dendrites are involved in the temporary maintenance of selected mental activities [16].

Selective attention in vision and predictive coding

Selective visual attention **modulates** the sensory-driven activation of neurons encoding the visual features or spatial location being attended [61–63]. Typically, neural responses to an attended stimulus are increased in amplitude and duration [64], while activity corresponding to non-attended stimuli is decreased [62,65,66]. Cortical feedback projections from higher regions [67–69] that target the apical dendrites in layer 1 transmit attentional signals to lower cortical regions processing visual input [61].

Given these long-established facts, it is surprising that most models of visual attention do not use neurons with a separate apical compartment, though there are a few that do [2,70–74]. Most models do not explicitly describe a neurophysiological mechanism through which attentional influences could be mediated, even though they assume that attentional signals have a distinct modulatory influence on the transmission of sensory signals. Hence, that can be envisaged as being implemented by amplifying transmission of information from the sensory input to the basal dendrites of pyramidal cells [75]. Other models of computation in human layer 2/3 cells have also been proposed [76].

This modulatory influence of attentional, top-down, signals has been modeled as a simple multiplicative amplification of the sensory signal [69,71]. Though simpler than the complex interactions between the apical and somatic compartments seen in biological pyramidal cells, it provides a first-order approximation to AA. Despite this simplification, these models can account for much neurophysiological data [71,77]. Furthermore, they can be extended to simulate interactions between attention and other contextual information transmitted by lateral connections within cortical regions to account for the neurophysiological observations of attentionally gated collinear facilitation [7] and of the incremental grouping of contour elements [74].

In these models, the increase in activity corresponding to attended stimuli is due to top-down amplification, while suppression of activity corresponding to unattended stimuli results from intra-regional competition between neurons representing competing signals. These models can

therefore be considered as implementations of the biased-competition theory of attention [66]. Different forms of competition have been proposed. If competition is mediated via distinct populations of error neurons, these models can also be interpreted as implementations of a form of predictive coding in which top-down, modulatory signals, target the apical dendrites of prediction neurons [77,78]. Models of this kind can account for many aspects of endogenous and exogenous (involuntary) attention [79].

Alternative, and more widely known, models of predictive coding [80,81] equate 'error neurons' with superficial layer pyramidal cells. These neurons receive two distinct forms of top-down input: predictions and precisions [82–85]. Predictions are assumed to have an inhibitory influence, which is inconsistent with observed facilitatory influences of cortical feedback connections to apical dendrites [30,37,86]. Precisions are assumed to have a modulatory influence, so if that implies a reweighting that gives predicted inputs more importance it might make those models compatible with the evidence for AA. In those alternative models, however, precision targets error neurons that are assumed to be active only when sensory input has not been correctly predicted. Hence, those models are not easily reconciled with our understanding of selective attention because they seem to imply that only unpredicted stimuli can be attended. Several rigorous reviews do cite much evidence for predictive error coding (e.g., [82]), but it remains to be seen how that evidence is best reconciled with the evidence for **cooperative interactions** that seek agreement rather than error [37]. We assume reconciliation to be possible because maximizing prediction success implies minimizing prediction error (though not vice versa).

Though overlooked by 20th-century psychology and systems neuroscience, communication between distal apical dendrites and soma within context-sensitive cells is restricted to being positive, as are axonal signals. In both cases, the activity-dependent ionic mechanisms on which they depend are excitatory; we know of no negative apical or axonal spikes. This has far-reaching implications for predictive coding theories. It contradicts those that rely on feedback to layer 1 to inhibit cellular output. Though it might be suggested that feedback closer to the soma may provide the suppression or subtraction assumed that would inextricably combine the feedback with the basal/perisomatic inputs about which the cell transmits information, so it would not be modulatory [29]. To see how these difficulties can be resolved, note that the intensity of a radio's output can be attenuated by turning down the amplification. Similarly, cellular responses to an input can be attenuated by reducing the amplification that would otherwise occur. Furthermore, output intensity can be either increased or decreased without changing the cell's selective sensitivity, which is analogous to changing the intensity of a radio's output without changing the channel to which it is tuned. Thus, AA can be seen as a mechanism for controlling output intensity without changing tuning [37].

Contextual disambiguation and visual illusions

Sensory information is often ambiguous or impoverished. In those cases, disambiguation, filling-in, or erroneous percepts often arise in ways that depend on context. Context-sensitive cells provide a mechanism for disambiguation by amplifying cellular activities that convey the selected percept based on contextual input to their apical dendrites (Figure 1). Similarly, if mutually incompatible responses are suggested by low quality sensory input or structural ambiguity, then selection by contextually pertinent apical activation would overcome that impasse (Box 1). This is fundamentally different from experimental paradigms that compare brain responses recorded in trials that are either above or below the threshold for subjective experience [87]. Furthermore, when the perceiver is biased by habitually expected context, apical activation may be so strong that apical drive leads to deceptive experiences, including hallucinations or false alarms in psychophysical tests of perceptual awareness [4,88].

Expectation-dependent perceptual enhancement has been directly demonstrated using partially occluded difficult-to-recognize two-tone images of faces, animals, and landscapes. fMRI recordings, discussed further later, show that prior knowledge of those images adds detailed stimulus-specific feedback to the representation in early visual areas when seeing subsequent presentations of those images [89].

Moreover, when there is a strong association between an object O and a specific context C, an encounter with C is sometimes sufficient by itself to elicit a fictive percept of O [88,90,91]. Cellular context-sensitivity provides a mechanism for those hallucinatory fictive percepts. Sufficiently strong apical input from memory could produce cellular output by itself in the absence of the feedforward sensory information, transmission of which would usually be amplified if it were present in that context. As noted, that may require exceptionally high levels of apical activation [48]. That hypothesis is supported by the finding that direct artificial stimulation of the **apical integration zone (AIZ)** in awake mice can produce false alarms as if they were hallucinating the presence of an absent external stimulus [4,88].

In addition to these studies of disambiguation and illusion, there are many other ways in which cognitive consequences of cellular context-sensitivity have been or could be studied [5–15], including the neuroimaging discussed next and as recently outlined in a synthetic overview [16]. Countless Gestalt demonstrations show that perception depends on context, including many illusions. Emphasizing illusions can be misleading, however, because context-sensitivity often enhances perception, as outlined in Box 2, which lists a few of the many ways in which cognitive consequences of cellular context-sensitivity can be explored.

Layer-specific neuroimaging of context-dependent perceptual inference

Non-invasive functional brain imaging provides a way of bridging the gap between mechanisms studied in animals and processes observable in humans. With brain imaging, the first empirical

Box 2. Exploring cognitive consequences of cellular context-sensitivity

Consider context-sensitivity of size perception, for example. In specially designed displays it causes the Ebbinghaus illusion, but rigorous psychophysical studies show that when it is a valid cue it enhances discrimination [124–126]. Those studies show that the strength of context-sensitivity depends on sex [124], age [125], culture, and cognitive style [126]. As it operates rapidly and automatically and as the variables on which it depends are as expected if it involves cellular context-sensitivity, that possibility now merits further exploration.

Studies using priming, masking, and the attentional blink also indicate that the spatiotemporal contexts in which stimuli are presented have large effects on detection, discrimination, and recognition [127–130]. In studies of visual backward masking, subjects' reports indicate that they did not see a briefly presented target followed too soon by a masking stimulus [129]. Dendritic integration theory [6,7] suggests an explanation because it implies that awareness requires a minimum duration of amplification. Thus, according to that explanation, if the mask arrives before amplification of the flashed target has occurred then amplification of stimulation at that spatial location produces awareness of the mask instead of the target. Investigations of this possible explanation could use transcranial magnetic stimulation or other techniques to suppress or enhance amplification at specific times relative to target and mask presentation. Furthermore, as priming by a pre-target stimulus reduces susceptibility to masking [128,129], prior artificial activation of distal apical dendrites should reduce masking, according to dendritic integration theory. Priming by subliminal masked stimuli also merits exploration, because, as amplification is not necessary for feedforward transmission, there are likely to be circumstances in which it occurs.

The attentional blink occurs when two targets (T1 and T2) of a specified category (e.g., numbers) are presented in a stream of rapid successive presentations of non-target category items (e.g., letters) [130]. Presentation frequency is typically 10 Hz. If T1 and T2 are presented in successive frames, the subject is aware of both. If T2 follows T1 after some 300–500 ms, however, something peculiar happens. Even though the time and number of intervening events between the two targets is increased, T2 is not consciously perceived if T1 was consciously perceived. AA offers a possible explanation if awareness requires presence in WM for at least 300–500 ms. As WM capacity is severely limited the attentional blink may occur because WM is being used to amplify and maintain T1 when T2 is displayed.

problem is to isolate contextual influences from feedforward-driven responses. One paradigmatic solution takes advantage of the retinotopic organization of primary visual cortex (V1) and records activity in parts of that region receiving no feedforward sensory input because of some occlusion within the current scene [92]. For example, when humans view partially occluded scenes during fMRI, the visible scene content provides a contextual signal that can be read out from the retinotopic V1 regions sensitive to the occluded region of sensory input [3,93–96].

Using advanced human neuroimaging and animal models [97], contextual effects during partial visual occlusion have been replicated in humans, monkeys, and mice [98] and are yielding insights into context-sensitive cognitive capabilities and the cellular mechanisms on which they depend. In cross-species comparisons, the visual occlusion paradigm has been used to control the context provided by the visible part of the scene. In human studies, the context studied has also come from other senses, from memory, the current task, or emotional context. For example, when subjects are blindfolded, sound processing provides contextual input to visual cortex [99,100].

Using high-resolution fMRI at ultra-high magnetic field strengths it is possible to distinguish activity in superficial locations proximal to the pial surface from that in deep layers [101], though even greater layer-specificity would be helpful. Because of its sensitivity to small fluctuations of post-synaptic dendritic membrane potentials fMRI can reveal contextual influences in human cortex non-invasively and during complex behavioral tasks [102]. During partial visual occlusion, contextual signals are detectable in superficial layers of cortex [3], in line with the evidence from cellular neurophysiology. That is consistent with the morphology of pyramidal neurons with apical dendrites in upper cortical layers receiving modulatory input from diverse sources, including feedback or top-down projections from higher regions [17]. Numerous other paradigms investigate high levels of activity in the superficial and/or deep layers of V1 that receive contextual inputs from diverse sources including feedback (Figure 2). These include high-resolution imaging during WM [103], feature-based attention [104], spatial attention [105], cross-modal influences (see [106]), visual illusions [107,108], memory (with 3T fMRI) [109], mental imagery [108], and motion perception [110]. In the specific case of visual occlusion, contextual signals might be related to predictions of the missing scene features, as generated from internal models developed through prior experience [95].

It must be noted that there is also evidence that prior expectations evoke stimulus-specific activity in the deep layers of V1 [111]. The significance of those findings for cognition is a major issue for future research. That should include distinguishing feedback to basal or perisomatic locations on layer 5 cells from projections to either deep interneurons or the short apical dendrites of L6b cells. The latter would entail enhancing amplification via the apical tufts of cells in layers above layer 6 because that is one of the effects of L6b activation.

Relations of neuroimaging findings to cellular morphology and context-sensitivity now require intensive study. One issue on which macroscopic neuroimaging could throw light concerns the possibility that sensitivity to context increases with level of abstraction [112,113]. Another potentially large and medically important sub-field of cellular psychology relates cellular context-sensitivity to psychopathology. Laminar brain imaging is already helping to constrain proposed theories of predictive processing in psychosis [114]. Neuroimaging could also be used to explore changes in context-sensitive predictive processing observed in many neurocognitive disorders [12,14,115,116]. Such explorations are encouraged by the mapping of unbroken paths from initiating causes to cognitive consequences via impaired cellular context-sensitivity in Fragile X, Down syndrome, and fetal alcohol spectrum disorders [15].

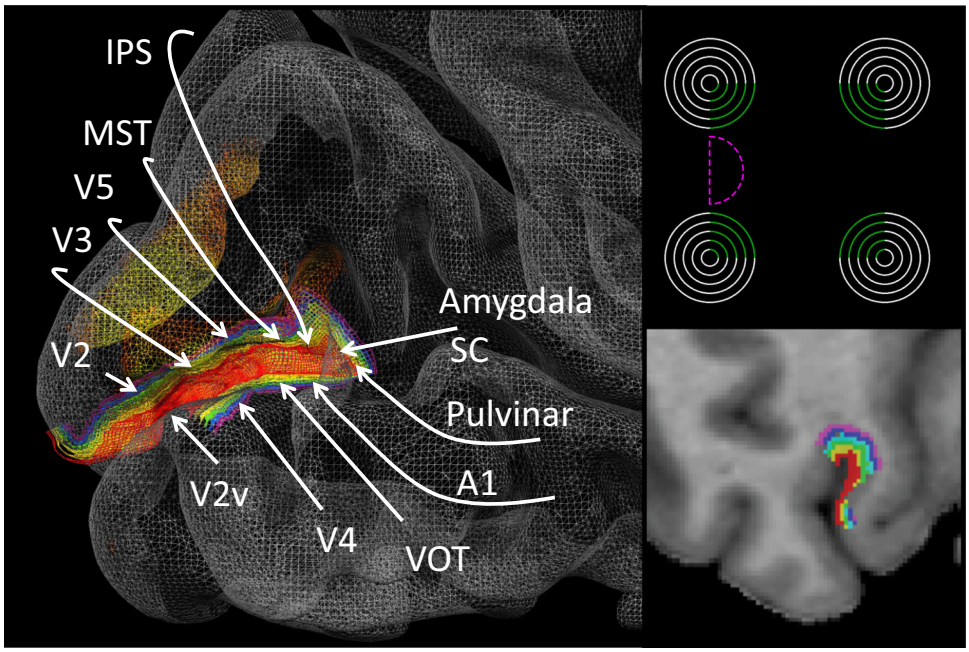

Figure 2. Layer-specific macroscopic neuroimaging of context-sensitivity. Left: schematic showing diverse contextual inputs to V1 [17,92]. In many cases, direct connections are known to arrive at superficial layers. Rainbow colors sequentially depict reconstructed depth layers from deep locations proximal to the white matter (purple) to superficial locations proximal to the pial surface (red). They are shown on a cortical grid mesh of the left hemisphere of a human participant. All sources project to all parts of V1. Right (upper): the neon color-spreading illusion used to study cortical depth profiles when experiencing imagined or illusory contours. When viewing this stimulus people typically experience green contours completing a whole green square even though no such contour is physically present [108]. Right (lower): ultrahigh-resolution fMRI at 7Tesla relates these illusory contours to information in the superficial layers of V1, and specifically in that part of the visual field where the illusory contour is seen (i.e., in the region shown by the pink dashed-line in the upper figure). As above, the grey matter is shown segmented into six cortical depth layers. Abbreviations: IPS, intraparietal sulcus; MST, medial superior temporal area; SC, superior colliculus; VOT, ventral occipito-temporal cortex.

Outstanding questions

Do context-sensitive cognitive capabilities of species without six-layer neocortex, such as birds or reptiles, depend on context-sensitive cells?

What is the cellular psychology of episodic memory, language, and the human imagination?

To what extent does cellular psychology validate neuroconstructivist views of cognitive development?

What are the similarities and differences between cellular psychopathology and cognitive neuropsychology?

Will cellular psychopathology change attitudes to cognitive disabilities and lead to engineered combinations of pharmacological and psychological therapeutic strategies?

What philosophical implications does cellular psychology have – if any?

Concluding remarks

Since being related to consciousness [6], studies of the information processing capabilities of cooperative context-sensitive pyramidal cells with two functionally distinct sites of input integration have been gathering momentum. The findings reviewed here can be seen as the early stages of a new field of research into the implications of those capabilities for psychology, neuroscience, psychiatry, neurology, philosophy, and beyond. Many new key issues arise (see Outstanding questions). Gordon M. Shepherd, a renowned neurobiologist, proposed that this new field be called ‘cellular and psychological neuroscience’ (personal communication). Even more briefly it could be referred to as ‘cellular psychology’ [16].

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Declaration of interests

No interests are declared.

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