



Cognitive functions of intracellular mechanisms for contextual amplification



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ARTICLE INFO

Article history:

Received 21 May 2015
Revised 16 September 2015
Accepted 18 September 2015
Available online 1 October 2015

Keywords:

Apical amplification
Disamplification
Contextual modulation
Consciousness
Cognition
Neocortical computation

ABSTRACT

Evidence for the hypothesis that input to the apical tufts of neocortical pyramidal cells plays a central role in cognition by amplifying their responses to feedforward input is reviewed. Apical tufts are electrically remote from the soma, and their inputs come from diverse sources including direct feedback from higher cortical regions, indirect feedback via the thalamus, and long-range lateral connections both within and between cortical regions. This suggests that input to tuft dendrites may amplify the cell's response to basal inputs that they receive via layer 4 and which have synapses closer to the soma. ERP data supporting this inference is noted. Intracellular studies of apical amplification (AA) and of disamplification by inhibitory interneurons targeted only at tufts are reviewed. Cognitive processes that have been related to them by computational, electrophysiological, and psychopathological studies are then outlined. These processes include: figure-ground segregation and Gestalt grouping; contextual disambiguation in perception and sentence comprehension; priming; winner-take-all competition; attention and working memory; setting the level of consciousness; cognitive control; and learning. It is argued that theories in cognitive neuroscience should not assume that all neurons function as integrate-and-fire point processors, but should use the capabilities of cells with distinct sites of integration for driving and modulatory inputs. Potentially 'unifying' theories that depend upon these capabilities are reviewed. It is concluded that evolution of the primitives of AA and disamplification in neocortex may have extended cognitive capabilities beyond those built from the long-established primitives of excitation, inhibition, and disinhibition.

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1. Introduction

Neocortical function depends on inference – inferences about distal things from proximal signals, inferences about the implications of symbolic propositions or beliefs, and inferences about the likely consequences of possible actions. As these inferences are often probabilistic and dependent upon the particular context in which they are made, neural systems must combine context-sensitivity with the dynamic coordination of many widely distributed local neuronal inferences, and ways in which this may be done are a topic of intense investigation (e.g. von der Malsburg, Phillips, & Singer, 2010). It is now well-established that this coordination involves various forms of contextual modulation (e.g. Lamme, 2004; Salinas & Sejnowski, 2001). Some amplify and group relevant activities; others suppress irrelevant activities. Sherman (2012) reviews physiological evidence showing that there are two clearly distinct classes of thalamocortical and corticocortical synaptic interaction; one is driving, the other is modulatory.

Gilbert and Sigman (2007) review neurophysiological studies of top-down modulation in relation to sensory and higher processes. The functions, mechanisms, and malfunctions of contextual modulation in general have been reviewed recently (Phillips, Clark, & Silverstein, 2015), so this paper is focussed specifically on intracellular mechanisms that amplify response to driving inputs and on the cognitive functions that they are thought to have.

It has often been argued that, though there are important variations, similarities in microcircuit anatomy and physiology across regions and species suggest that there may be a common (i.e. much used though not necessarily ubiquitous) neocortical strategy by which diverse types of information are processed, including those involved in sensation from diverse modalities, motor control and higher cognitive processes. For an assessment of this issue by many expert commentators see Phillips and Singer (1997). For a recent in-depth review supporting such arguments see Harris and Shepherd (2015). It has also been argued that these commonalities include regions classified as affective as well as those classified as cognitive (Pessoa, 2008), regions that are concerned with the theory of mind as well as those that perform basic sensorimotor

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functions (Ondobaka, Kilner, & Friston, 2017), and regions concerned with phenomenological experiences such as the conscious sense of presence (Seth, 2013; Seth, Suzuki, & Critchley, 2011). So, how could a common information processing strategy serve such a wide variety of different purposes? As answers to this question cannot be framed using concepts specific to each of the domains of application they must be framed using more abstract concepts, such as those of information theory (Kay & Phillips, 2011; Wibral, Priesemann, Kay, Lizier, & Phillips, 2017) and probabilistic inference (Fiorillo, 2012; Friston, 2010; Phillips, 2012).

Common abstract goals that are of most relevance to the intracellular mechanisms reviewed here can be described informally as amplifying and grouping signals that are relevant in the context of current activity elsewhere and as suppressing signals that are irrelevant. The concept of ‘grouping’ referred to here is that of dynamic grouping as defined by Phillips, von der Malsburg, and Singer (2010) which is a refined version of the notion of ‘binding’ and which is similar to the concept of ‘temporary coalitions’ (Crick & Koch, 2003). Section 4 outlines theories that express these goals as a formal objective for neural systems composed of local cortical processors that receive two functionally distinct sources of input: driving input from which the information to be transmitted is selected; and modulatory input that conveys contextual information that amplifies, suppresses, and coordinates responses to the drive. The central hypothesis examined here is that modulatory mechanisms within pyramidal neurons of the neocortex provide computational capabilities that this requires. This hypothesis contrasts with the common assumption that the neural bases of cognition can be adequately understood in terms of integrate-and-fire point processors. Such point processors sum their excitatory and inhibitory inputs and transmit a signal when that sum exceeds a threshold. Assuming that neurons function as point processors is useful in that it frees cognitive theorists from any need to grapple with the many complexities of intracellular processes. That assumption is misleading, however. The evidence reviewed here clearly indicates that perception, thought and action may be more correctly, and more economically, understood as involving pyramidal cells that, in addition to the somatic integration site for driving inputs, have a distinct apical integration site for modulatory inputs, with far-reaching consequences for cognition.

The conception of ‘contextual modulation’ on which this paper is based was first defined rigorously by Phillips, Kay, and Smyth (1995). Further refinements and implications of that neuron-centric conception are discussed at length by Phillips et al. (2015, Section 2). The most recent development in this perspective on contextual modulation builds upon recent advances in information theory. Those advances extend information theory beyond the case of mutual information between input and output variables, and provide general definitions of unique, shared, and synergistic components of transmitted information for the case of multiple inputs. For a formal presentation of that advance and its relevance to contextual modulation see Wibral et al. (2017). In essence, modulatory inputs are distinguished from driving inputs on the grounds that, whereas driving signals can produce an output by themselves, the effects of modulatory inputs are conditional upon the presence of a primary driving signal to which response is modulated. A key information-theoretic criterion for this modulation is that information transmitted uniquely about the modulator increases as the strength of another input variable (i.e. that to which response is modulated) is increased from zero (Phillips & Craven, 2000; Smyth, Phillips, & Kay, 1996). If the strength of the driving receptive field input is denoted by R , the strength of the modulatory contextual field input by C , and the output strength by Y then a simple form of contextual modulation is $Y = R + RC$. This contains the necessary asymmetry between R and C because R can then

produce an output when $C = 0$ but C cannot produce an output when $R = 0$. It also distinguishes this form of contextual modulation from a purely multiplicative interaction in which $Y = RC$. In that latter case the multiplicative interaction is not amplifying a response that signals the presence of R but is computing the value of a new variable that requires the presence of both R and C , as in coordinate transformation, for example (Phillips & Silverstein, 2013). See Section 4.3 for further discussion of this issue.

As the focus of this paper is on modulatory interactions within the neocortex it is important to see how they are related to the well-known effects of the classical neuromodulators, such as norepinephrine, and dopamine. The fundamental difference between modulatory interactions within the neocortex, such as those implemented by AA, and modulation of cortical activity by sub-cortical neuromodulators is that, whereas sub-cortical modulation is diffuse, intrinsic modulatory interactions, such as AA, are far more specific, thus enabling the context-sensitive selection of particular percepts, thoughts, and actions. These intra-cortical modulatory interactions may be of especial importance to human cognition, which seems to excel in such context-sensitive flexibility. As our understanding of locally specific intra-cortical modulatory processes grows many questions will arise concerning their interaction with diffuse neuromodulation.

The following sections are organized as follows. Section 2 summarizes direct and indirect evidence indicating that some classes of pyramidal cell have intracellular mechanisms for context-sensitive amplification, and that particular types of inhibitory interneuron have evolved to specifically regulate that amplification. Section 3 outlines various cognitive functions to which these mechanisms are thought to contribute. It also outlines a few of the many psychopathological disorders arising from their malfunction. Section 4 clarifies what is meant by ‘unifying’, and re-assesses some potentially unifying theories of cortical computation in the light of the evidence for AA. Section 5 lists some of the many unresolved issues that arise.

2. Intracellular mechanisms for contextual amplification

Structure often provides a clue to function (Crick & Koch, 2003), so this section first seeks clues in pyramidal cell morphology and in aspects of long-range connectivity. Direct intracellular evidence supporting the inferences drawn from these clues is then reviewed. It suggests that input to synapses in layer 1 can amplify pyramidal cell responses, and that specific inhibitory mechanisms have evolved to regulate that amplification.

2.1. As inputs to the apical tuft are electrically remote from the soma they could have evolved modulatory capabilities

Pyramidal cells of the neocortex have an apical trunk that ascends from the cell body, or soma, to a dendritic tree called the apical tuft. If their soma is in layers 2, 3, or 5 then the tuft is in layer 1 of the cortex. If the soma is in layer 6 then the tuft is in layer 4. Tuft dendrites are richly studded with synapses but they are electrically remote from the soma. Without active dendritic mechanisms the effects of synaptic input to the tuft would be so strongly attenuated at the soma that they would have little or no effect on action potential generation (Häusser & Mel, 2003). The apical trunk must therefore have mechanisms for active signal propagation. They may include mechanisms that compensate for the distance of the tuft in a way that enables it to contribute to a ‘dendritic democracy’ in which all synapses have an approximately equal opportunity to contribute to the cell’s output (Häusser & Mel, 2003; Magee & Cook, 2000; Williams & Stuart, 2003). Thus, the morphological asymmetry between basal and tuft dendrites does

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