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Moving Sensory Adaptation beyond Suppressive Effects in Single Neurons

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Abstract

How an object is perceived depends on the temporal context in which it is encountered. Sensory signals in the brain also depend on temporal context, a phenomenon often referred to as adaptation. Traditional descriptions of adaptation effects emphasize various forms of response fatigue in single neurons, which grow in strength with exposure to a stimulus. Recent work on vision, and other sensory modalities, has shown that this description has substantial shortcomings. Here we review our emerging understanding of how adaptation alters the balance between excitatory and suppressive signals, how effects depend on adaptation duration, and how adaptation influences representations that are distributed within and across multiple brain structures. This work points to a sophisticated set of mechanisms for adjusting to recent sensory experience, and suggests new avenues for understanding their function.

Introduction

Adaptation affects how neurons respond to sensory stimuli, making them sensitive to the temporal context in which a stimulus is embedded. Adaptation thus adjusts brain processing to the current sensory environment, and it is generally thought that this improves performance in some way. Understanding how the brain adapts may therefore provide insight into its computational goals, and the constraints on its functional organization. Adaptation is also of interest because it is widely used in human functional imaging and perceptual studies to infer the selectivity of neurons and brain areas, and to deduce the computations involved in sensory processing. Proper inference in these domains requires a thorough understanding of how neurons and circuits adapt.

Early descriptions of adaptation effects emphasized fatigue of single neurons during the presentation of an effective stimulus. In mechanistic terms, these effects can be explained by

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the observation that adaptation shifts a neuron's state away from the threshold required for generation of action potentials [1–7]. This hyperpolarization is triggered by intrinsic mechanisms that are recruited during periods of high activity [2–4]. There are four central tenets that follow from this description and our understanding of the mechanisms responsible: first, it takes time for neurons to recover from periods of high activity, and neurons therefore show reduced responsiveness to subsequent stimuli; second, fatigue is more pronounced when an adaptor is presented for longer durations; third, the degree of fatigue depends on the effectiveness of the adaptor, so a stimulus that matches a neuron's preference will cause the strongest effects; and fourth, because it involves simple fatigue, adaptation will reduce sensitivity to all subsequent stimuli, not just those that resemble the adaptor.

The simple fatigue description fails to capture the stimulus specificity of adaptation effects: responses to stimuli that resemble the adaptor are reduced more than responses to stimuli that differ from it. When the adaptor falls on the flank of the tuning curve, this specificity causes the neuron's tuning to shift away from the adaptor [8–11]. Stimulus-specific adaptation effects can be accounted for by synaptic fatigue, which results in less synaptic input from neurons whose stimulus preference best matches the adaptor, either because these presynaptic cells are fatigued or because transmitter release from their terminals is depressed [12,13].

Stimulus-specific fatigue cannot explain all adaptation effects (see [14–20] for reviews). For instance, adaptation with dynamic stimulus sequences have revealed that neuronal input–output functions can adjust to encode the range of stimuli in the environment [21,22]. Nevertheless, the stimulus-specific fatigue description has provided a powerful and simple explanation for many physiological and perceptual observations [14–17,20], and is central to a number of functional proposals [9,23].

More recent work has revealed limitations of fatigue-based descriptions of adaptation effects, evident even in the simplest adapt-test paradigm. Our aim here is to highlight the emerging themes of this work. First, we will review evidence that adaptation can enhance responsivity, not just reduce it. Many of these facilitory effects of adaptation can be explained and predicted by invoking normalization, a widely observed component of sensory processing. Second, it is now clear that there is a complex relationship between adaptation duration and the effects it induces — and that one cannot assume that longer adaptation simply causes stronger effects. Third, recent work has begun to move beyond exploring effects in single neurons at discrete stages of processing, to studying how adaptation alters representations distributed within and across stages of processing. We will discuss how together this work reinvigorates, and informs, the search for a clear functional benefit of adaptation effects. We will focus on the visual cortex where much of this work has been performed, and draw parallels in other systems where available.

Normalization and Adaptation in Visual Cortex

The receptive fields of sensory neurons consist of two distinct components. The first is the classical receptive field (CRF), which defines the stimuli that can directly drive spiking activity. For example, the CRF of a simple cell in primary visual cortex (V1) can be

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approximated by a linear filter, which determines selectivity for stimulus parameters such as position and orientation, and an output nonlinearity, which relates filter responses to spiking activity. The simple fatigue description of adaptation is captured by a change in the nonlinearity, thus affecting responses to all stimuli (Figure 1A); changes in tuning preference caused by stimulus-specific fatigue are captured by altering the shape of the filter (Figure 1B).

The second component of the receptive field is composed of 'gain-controls', or normalization signals (Figure 1C, left). These inputs have a divisive effect on the output of the CRF and thus suppress spiking activity. Normalization signals have been observed across sensory modalities, and are an integral component of modern functional models of sensory neurons [24]. Normalization signals are generally recruited by a broader range of stimuli than those that drive the CRF — a working description is that normalization arises from the activity of a pool of neurons, with a broad range of functional properties and receptive fields that can either spatially overlap the CRF of the target neuron or be offset from it. Normalization explains why there is sub-linear summation of responses to two sensory stimuli within the CRF, as in masking and contrast saturation. It also explains why large stimuli, which recruit normalization from the 'surround', evoke weaker responses than stimuli falling wholly within the CRF.

Recent work has shown that adaptation not only affects the CRF, but can also weaken normalization signals (Figure 1C, right). Because normalization is suppressive, weakening these signals is a form of disinhibition, which can enhance responses to subsequent stimuli. A clear example of such facilitation is evident when an adaptor is placed in the surround. Such adaptors elicit no response from the CRF, by definition, but do weaken normalization signals from the surround. As a result, responses to stimuli that cover both the CRF and surround are enhanced after adaptation of the surround (Figure 2A), in some cases by two- or three-fold [25,26].

Weakened normalization signals can also shape the effects of adaptation on neural tuning. Adaptation weakens normalization in a stimulus-specific way, yielding a tuned disinhibition, just as the specificity of its effects in the CRF results in tuned fatigue. Tuned disinhibition, in turn, results in maintained or enhanced responses to stimuli similar to the adaptor (see Box 1 for further discussion). Such effects have been observed in V1, where a large adaptor causes orientation tuning to be attracted towards the adapting orientation (Figure 2C) [11,26,27]. Adaptation can cause similar attractive shifts in V1 colour tuning (Figure 2D) [28], and direction tuning in visual cortical area MT [29,30].

The effect of adaptors that provide drive to the CRF and normalization pool depends on the relative sensitivity of these two receptive field components to the adaptor and test. Responsivity will be reduced most when the adaptor provides strong drive to the CRF (Figures 2E,F), and weak drive to the normalization signals. Previous single neuron studies of adaptation have emphasized reduced responsivity because they usually tailored stimuli to match the CRF of the recorded neuron. In these cases, adaptation effects on the CRF overwhelm those on normalization signals. By contrast, an adaptor that strongly drives normalization signals, but is only moderately effective for the CRF, is likely to have facilita-

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tory effects. For instance, adaptation to a grating that is within the CRF but orthogonal to a neuron's preferred orientation will weaken normalization signals (Figure 2G,H; [31] but see [32]). If the tuning of the CRF is sufficiently narrow [33], orthogonal adaptors will then enhance responsivity [26,31]. Importantly, because normalization signals are more broadly tuned than the CRF, the effects of an adaptor on normalization signals will likely be evident in a larger population of neurons than are its effects on CRFs.

The normalization framework also explains how stimulus intensity can influence the effects of adaptation. The framework predicts that responses to weak test stimuli should be reduced particularly strongly after adaptation. These test stimuli do not recruit substantial normalization; thus, the impact of any adaptation-induced changes in normalization will be limited. Responses to high-intensity test stimuli, on the other hand, may be only slightly reduced by adaptation, or even enhanced, as recently reported (Figure 2G) [26,31,34]. This reasoning can also explain why repeated presentations of weak stimuli result in a greater loss of responsivity than repeated presentations of strong stimuli [30]. The relationship between stimulus intensity and normalization signals also predicts that the effects of adaptation on tuning should depend on test stimulus intensity: adaptation should repel tuning for low-intensity stimuli, but attract tuning for high-intensity ones. These points are discussed further in Box 1.

While the normalization framework can predict the relative strength of adaptation effects for different stimuli, the absolute strength of effects will also depend on the baseline against which the adapted state is compared. Frequently, the baseline involves stimuli presented in temporal isolation (that is, separated by long presentations of a blank screen). Such a state is highly unusual: in our everyday experience, stimuli appear in a steady stream [35,36]. Whether recent experience facilitates or suppresses neural responses under continuous sensory stimulation will depend on the change it induces in the ongoing adaptation state of both the CRF and normalization signals. For instance, even traditional descriptions would predict a relative enhancement of responsivity, if responses after an ineffective adaptor are compared to a baseline of greater fatigue [26].

In summary, recent work has shown that adaptation can have a diverse set of effects on neuronal tuning. Adaptation can sensitise or desensitise sensory neurons, deform tuning towards or away from the adapted stimulus, and also leave responsivity unaltered. These diverse effects can nevertheless be explained in a straightforward way: that is, by allowing normalization signals to be adaptable, and by understanding how an adaptor and subsequent test stimuli engage the CRF and normalization pool.

Adaptation-induced Disinhibition Outside Visual Cortex

We have so far focused on work in visual cortex, but research in other brain areas and sensory systems has revealed similar evidence of adaptation-induced disinhibition. Normalization may be a canonical computation [24], so these effects might also be explained within this framework. Nevertheless, because the concept of normalization has been applied less broadly in other systems, we will refer to these findings in more general terms — as examples of adaptation-induced changes in the balance between excitatory and suppressive signals.

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In the retina and lateral geniculate nucleus (LGN), adaptation to a small stimulus that lies within the CRF can lead to a substantial reduction in responsivity [37–39]. Adaptation of suppressive signals that lie outside the CRF usually enhances responses to stimuli that cover the CRF and the surround, just as in visual cortex (Figure 2B) [38,40]. Unlike the effects of adaptation on the visual cortex, however, those in the retina and LGN have limited stimulus specificity [38,40], except for spatial location [38,40,41].

Retinal circuits can be systematically explored *in vitro*, allowing for detailed investigation of the mechanisms underlying adaptation effects. Recent *in vitro* work has revealed how adaptation alters excitatory and inhibitory signals in the retina. Adaptation usually reduces the excitatory synaptic input to retinal ganglion cells, in large part by reducing the sensitivity of bipolar cell synapses [13,42,43]. Adaptation can also depress the activity of inhibitory amacrine cells, particularly those that use GABA as a neurotransmitter [3,41,43,44]. As a result, adaptation can reduce the responsivity of some ganglion cells and increase that of others, depending on the complement of excitatory and inhibitory inputs each cell receives. Indeed, recent work suggests there are distinct functional classes of retinal ganglion cells: one whose responses are enhanced by adaptation with high contrast stimuli, and another whose responses are reduced [41,45].

Many recent findings in the whisker somatosensory (‘barrel’) system of rodents also bear a striking resemblance to those in the visual system. Repeated whisker deflections have long been known to reduce neuronal responsivity in barrel cortex (for example [46]), but recently it has been found that this adaptation is also capable of increasing responsivity [47]. This enhanced responsivity has been attributed to inhibition being weakened more than excitation by adaptation ([48], but see [49]). Adaptation also reduces cross-whisker suppression, akin to a reduction in suppressive signals from the surround in visual processing [50]. Finally, adaptation with weak stimuli reduces barrel neuron responsivity more than adaptation with strong stimuli [51], as predicted by the intensity-dependence of normalization signals.

Timescales of Adaptation

The term adaptation traditionally encompasses exposure periods ranging from tens of milliseconds to tens of minutes. Within this range, traditional descriptions suggest that prolonging adaptation will increase the magnitude and duration of effects, but not their qualitative nature — sometimes termed ‘duration scaling’ [52]. Duration scaling is consistent with much previous work: for example, changes in neuronal contrast sensitivity can be induced within 50 ms [53], but are stronger and longer-lasting after more prolonged adaptation [34]. Although duration scaling provides a reasonable first-order description, recent work has shown a more complex and sophisticated relationship between adaptation duration and induced effects.

One violation of duration scaling arises because adaptation effects are shaped by the time course of normalization signals, particularly those from the surround. These signals are often delayed relative to those from within the CRF [54–56]. The effects of brief adaptation can dissipate so rapidly that the CRF may recover before normalization signals arrive. It follows that when adapting stimuli have an impact on normalization signals, brief and prolonged adaptation can generate qualitatively different effects [11,27].

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It is not certain that the CRF and normalization signals adapt at different rates, but there is evidence they might. For instance, receptive field size changes with presentation duration [57], suggesting effects on the CRF and surround are induced at different rates. Furthermore, the effects of high-intensity adaptors dissipate more rapidly than those of weak ones [51], perhaps because excitatory and inhibitory inputs recover at different rates [47]. Within the normalization pool, some elements may be more susceptible to adaptation than others [25,31,32]. Differences in induction or recovery rates may provide flexible time scales, the expression of which depends on both adaptation duration and how the adaptor recruits CRF and normalization signals. Because of this interaction, duration scaling is likely to provide a poor description of how effects depend on adaptation duration. However, models that incorporate distinct duration scaling rules for different sources of excitatory and suppressive signals may provide a straightforward explanation for these seemingly complex phenomena.

Duration scaling is associated with the idea that adaptation effects can be explained by a single fatigable mechanism, with a single time course. Recent work has revealed instead that cortical networks, and even individual neurons, can store multiple timescales of adaptation simultaneously [4,58–60]. Perceptual studies have revealed similarly sophisticated behaviours. Adaptation to an oriented pattern induces a robust tilt aftereffect, in which the perceived orientation of a test stimulus is repelled away from the adapted orientation [17]. If the adaptor is presented for four hours, a tilt aftereffect persists for tens of minutes. This aftereffect can be entirely reversed by 15 minutes exposure to natural images; however, this reversal dissipates quickly, and the aftereffect of the initial, prolonged adaptor, reappears [52]. This reappearance strongly suggests the simultaneous storage of the two aftereffects in a common neural substrate, each with a different degree of persistence (see also [61–63]).

In addition to the flexibility that is afforded by storing multiple timescales simultaneously, these timescales may themselves be modifiable. Organisms are sometimes confronted with environments in which statistics change slowly, but at other times the environment changes rapidly and frequently. A sensible strategy may be to yoke the time course of adaptation effects to the temporal constancy of the environment. Consistent with such a strategy, recordings from ganglion cells in mouse retina show that frequent switches between low and high contrast stimuli are associated with faster adaptive changes in response than those that occur with less frequent switches ([64], see also [21,60]). These observations parallel those in motor control, where the timescale of motor adjustment depends on whether errors arise from transient or more persistent disturbances [65].

Finally, we note that the simple fact that adaptation refers to an enormous range of timescales poses an inherent challenge to the duration scaling description. The broad range of timescales implies an ensemble of cellular and circuit mechanisms. For instance, measurements of rapid adaptation can involve exposures of brief stimuli in immediate succession. In these paradigms the adaptor and test may both fall within the integration time window of a neuron (~100 milliseconds; for example [66]). Effects on such brief timescales may thus reflect static properties of temporal integration rather than plastic changes in neural circuitry [67]. At the other extreme, some adaptation effects last for days [61], and these may be better framed as semi-permanent adjustments of cortical circuits, akin to long-term

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learning. For duration scaling to hold while recruiting such diverse mechanisms, they would all need to have similar consequences on neuronal responses. This seems unlikely.

In summary, recent work has falsified a central tenet of traditional descriptions: adaptation effects do not simply grow with adaptor duration. Rather, effects can be qualitatively different for brief and long periods of adaptation, and may depend on the relative drive provided to the CRF and normalization pool. In addition, multiple timescales of adaptation can be stored simultaneously, and these timescales may be plastic themselves.

Adaptation Effects Across Stages of Visual Processing

Much of the neurophysiological work on adaptation has focused on its effects on single neurons, at distinct stages of processing. Sensory processing, however, reflects the activity of neurons distributed both within and across brain areas. This distributed processing raises a number of critical questions. How does adaptation influence the coordination of population activity within a local network? Do neurons at multiple stages of processing each adapt to a sensory input, or are effects implemented at an early stage and then simply inherited by downstream networks? When effects are inherited, how does this influence the computations performed in the recipient network? In Box 2, we review evidence that adaptation alters population coordination, although findings remain too discrepant to draw conclusions about precisely how. Below we review progress in understanding how adaptation affects responses across stages of the visual hierarchy.

Neurons at nearly all stages of visual processing are affected by adaptation. In addition to the work in the retina, LGN, and V1 discussed above, recent studies have documented effects in higher areas such as V2 [33], V4 [68], MT [30,69–73], IT [74–77], and FEF [78], among others [16,20]. Are the effects observed in higher stages generated locally or inherited from earlier networks? One approach to answering this question is to record from earlier stages, and see whether adaptation effects there are similar in nature or magnitude. These comparisons can be surprisingly thorny, however; for example, adaptation-induced changes in contrast sensitivity were thought to arise in V1, because there was little evidence of altered sensitivity in the LGN [34,79]. Later studies revealed that adaptation can in fact change contrast sensitivity in many retinal and LGN neurons [38,40,80–82]. This discrepancy may be due to the existence of several pathways from retina to cortex, which are differently susceptible to adaptation [38,41].

Comparisons across areas are also hindered by the use of stimuli tailored to the preferences of individual neurons, which typically differ across stages of the hierarchy. This precludes a direct comparison of how different stages adapt to a particular stimulus. For example, previous work suggested that adaptation caused attractive shifts in MT direction tuning [29], but not in V1 [8–11]. Rather than reflecting a difference across areas, these findings can be explained by the use of large stimuli in MT (tailored to the large receptive fields of neurons there), and small stimuli in V1 (where receptive fields are smaller). Adaptation-induced shifts in tuning are in fact similar in V1 and MT, when measured with stimuli matched in size [30].

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An alternative approach to testing for inheritance is to measure the spatial specificity of adaptation effects. The spatial size of receptive fields increases along the visual hierarchy. Thus, if an adapter confined to one sub-region of a receptive field does not influence responses to stimuli presented to another sub-region, this suggests that effects are induced at an earlier stage, where receptive fields are smaller. This approach has provided evidence for inherited adaptation effects in the retina ([37], but see [67]), and for some [71,83] but not all effects in MT [84].

Understanding the relative contribution of inherited and locally-generated effects only begins to address the issue of cascading adaptation. Altering inputs to a network can generate a range of effects, which depend on the interaction between the pattern of adapted inputs and local recurrent circuitry [29,85]. The effects also depend on how adapted inputs are combined: in general, downstream networks are thought to produce new representations by precisely combining inputs from earlier areas and imposing non-linearities (Figure 3A; for example, [86,87]). When adaptation alters the pattern of inputs, it may disrupt the formation of new representations, unless there is appropriate compensation in the downstream network.

Two recent studies [39,73] suggest that circuits do not compensate for inputs altered by adaptation. First, the deformation of spatial receptive fields in mouse V1 can be explained by weakened inputs from the LGN and unaltered pooling of these inputs by V1 neurons [39]. Second, adaptation disrupts a form of motion selectivity observed in primate MT, and this can be explained by assuming that adaptation desensitizes some inputs from V1, but does not change how MT neurons combine those inputs (Figure 3B) [73].

While these observations provide evidence for limited compensation in the targets of adapted neurons, recent work also offers a counter-example. McClelland et al. [88] showed that LGN neurons display robust responses at the offset of a prolonged presentation of a static stimulus. In V1, this after-response is much smaller in magnitude and shorter in duration [89]. This suggests that there are mechanisms capable of compensating for the adaptation state of inputs, so that downstream networks need not slavishly follow altered inputs.

In parallel with this neurophysiological work, perceptual experiments have also provided evidence that many adaptation effects cascade. Most generally, the existence of maladaptive aftereffects — the tilt or motion aftereffects [17,90] — suggests that higher sensory representations cannot easily divine the adaptation state of earlier representations. Perceptual work has also shown that adaptation to a simple visual feature can disrupt the representation of more complex stimuli, perhaps because effects in early stages derail downstream computations. For instance, adaptation to line curvature — which presumably affects the early visual system — can alter the perception of global form [91] and the inferred emotion of cartoon faces [92,93]. Similarly, adaptation to low-level features such as luminance and contrast can give rise to percepts of illusory motion [94]. Indeed, many aftereffects of motion adaptation can be explained by a model in which adapted non-directional units cascade onto directional units [95].

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In summary, we now understand that adaptation effects cascade downstream, and can disrupt computations performed at later stages of processing. These findings raise challenges for understanding the function of adaptation-induced plasticity and for making appropriate inferences about sensory processing in imaging and perceptual studies. Yet many of these observations may be explained by relatively simple models in which downstream networks are ‘unaware’ of adaptation-induced changes in their inputs [96].

Functions of Adaptation

It is incongruous that we have learnt so much about the impact of adaptation on sensory systems, but still know little of the purpose of these effects. It is widely believed that adaptation effects are beneficial, but for many effects it is not clear how. An answer is critical for understanding adaptation, but it may also shed light on key questions in sensory processing. Knowledge of how sensory systems adjust to different environments seems fundamental to understanding the strategies of sensory processing and the tradeoffs they entail. The recent empirical progress reviewed above raises questions for some existing proposals (of the many put forth [14–20]), and offers new possibilities.

One long-standing proposal is that adaptation sharpens acuity (discriminability) either around the adaptor or for offset stimuli. This proposal has been contentious, and perceptual evidence for improved acuity has been difficult to obtain [16,20]. Measurements in visual cortex suggest that adaptation can improve the acuity of single neurons [8,9], but it is not yet clear how this translates to population performance (Box 2).

A second hypothesis is that adaptation reduces the redundancy of sensory representations. An efficient neural representation should utilise the full range of activity patterns that it can produce. When some stimuli are more common than others, a subset of possible activity patterns is overrep-resented, and the encoding capacity is underutilised. Barlow [23] suggested that stimulus-specific fatigue alters neuronal tuning so that the full range of a network's activity patterns are used to encode the environment. It is important to note that this strategy is optimal only under the assumption that sensory inputs are noiseless, and that noise in the system is the same before and after adaptation; more realistic assumptions of noise give rise to distinct adaptation strategies [97,98].

A recent study in cat visual cortex offers initial experimental support for the Barlow proposal [99]. Population responses to rapid sequences of oriented patterns were measured; the distribution of orientations over time was either uniform, or biased such that one orientation was more common than the others. The efficient coding hypothesis predicts that neuronal tuning should adjust to reduce the response correlations caused by some stimuli being more common than others, and this is the case for a range of stimulus biases.

Achieving an efficient representation is unlikely to be the sole goal of adaptation. As discussed above, when adaptation reduces normalization signals it can enhance responsivity and attract tuning curves towards the adaptor. This should preserve or enhance the representation of an adapter and stimuli like it, opposite to the effects that motivated Barlow's proposal. What potential alternative functions are suggested by considering adaptable normalization signals? One possibility is that the weakening of surround

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normalization signals by adaptation enhances spatial integration [50]. Another is that pathways with ‘sensitizing’ adaptation effects — due, for instance, to weakened inhibition — allow the system to ‘hedge its bets’ [45,51,100]. Reducing neuronal responsivity may be a good strategy in the face of strong inputs, but it leaves the system vulnerable: if the environment suddenly changes, weak signals will be undetected. By having some neurons that sensitize and others that fatigue, the system can function in both environments.

A final, intriguing possibility is that adaptation modulates stimulus salience. This possibility arises in part from the effects of adaptation on normalization. Normalization signals from the surround are thought to be important for salience [101,102]. Because adaptation can weaken these signals, the salience of objects will depend on their temporal context. Consistent with this suggestion, psychophysical studies have shown that adaptation improves performance in visual search tasks, by modulating the salience of objects [103,104]. Recent physiological studies have also provided intriguing examples of adaptation influencing stimulus salience, by highlighting stimuli that are novel. Retinal ganglion cells, for instance, generate strong responses when an expected stimulus is omitted from an established sequence [105,106]. Direction-selective neurons in fly show sensitized responses when peripheral regions of the CRF experience motion opposite to that recently encountered [107]. Finally, in primate superior colliculus, weak stimuli have been shown to generate surprisingly strong responses when these stimuli are unexpected [108].

These findings are consistent with the presence of mechanisms that boost responses to unexpected events. Novel events are also naturally highlighted by fatigue-related adaptation effects: stimulus-specific fatigue reduces responses to unchanging features of the environment, emphasizing novel stimuli [109]. Together these processes can be thought of as an alternative form of redundancy reduction, or of predictive coding: persistent or recurring inputs are discounted to highlight new ones. In audition, a role in novelty detection has been ascribed to both fatigue-based and more active mechanisms. Specifically, the auditory evoked potential is larger when a sound is presented rarely, or embedded in a sequence of different sounds, than when it is presented frequently — an enhanced response called the ‘mismatch negativity’ [110]. Many instantiations of the mismatch negativity can be explained by stimulus-specific fatigue [111,112], but other work suggests the mismatch negativity reflects a more sophisticated predictive scheme [113–115]. At the perceptual level, unexpected stimuli that are associated with a mismatch negativity are also detected more easily [115,116].

Lastly, modelling work suggests that, in fatigue-based predictive coding, persistent stimuli can be ‘explained away’ using strengthened normalization [23,117,118]. While there is limited empirical support for stimulus-specific fatigue arising from strengthened normalization at a mechanistic level [119,120], the impact on neuronal tuning might indeed be captured by the normalization framework we have proposed for understanding disinhibitory effects of adaptation. This raises the possibility that stimulus-specific fatigue (strengthened normalization) and sensitization (weakened normalization) may reflect complementary strategies, the former emphasizing ‘explaining away’ and the latter emphasizing ‘predicting’ [41].

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Conclusions

Our understanding of sensory adaptation has been greatly enriched by work over the last decade. We have learned that adaptation has an effect on both excitatory and suppressive signals, and its effects do not simply grow with adaptation duration. Furthermore, adaptation alters population coordination and its effects cascade through the stages of processing, influencing downstream networks in sometimes unexpected ways.

Adaptation effects are thus substantially more complex than suggested by traditional fatigue-based descriptions. Fortunately, much of this complexity may be explained by simple models of brain circuits that incorporate a normalization framework, and invoke fixed integration by downstream networks. In any case, it is now clear that understanding adaptation effects will require them to be interpreted in the context of modern functional models of sensory processing, rather than as occurring in isolated individual neurons.

This new knowledge means that existing experimental approaches may need to be re-evaluated. For instance, perceptual and human brain imaging work often assume that repeated presentations of a stimulus reduce responsivity in the relevant neurons [121]. The cascading of adaptation effects, the dependence of those effects on adaptation duration, and the possibility of facilitation due to weakened normalization signals all raise significant concerns about inferences based on this assumption.

The empirical progress we have reviewed also calls for more theoretical work. We need theoretical frameworks that explain the impact of adaptation on population responses including normalization signals, consider how these effects influence downstream processing, and generate predictions for how adaptation can improve performance. We must keep in mind that the functional benefit of a representational change at one stage may be offset by the disruption that it imposes on subsequent processing.

These new observations also offer exciting directions for future work. First, the interaction between normalization and adaptation suggests a role in modulating salience and in predictive coding. Second, the normalization framework of adaptation may also offer a way to explore its role in other cortical functions. This is because normalization underlies a broad range of computations [122], and has been invoked to explain aspects of cognition like attention [123,124] and decision-making [125]. Finally, determining how adaptation affects population representations — distributed both within and across stages of sensory processing — is likely to offer powerful tools for dissecting the functional architecture of sensory processing.

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Box 1 Adaptation in the context of normalization models

The normalization model provides a functional description of neuronal responses. It captures the classical receptive field (CRF) as a weighted sum of driving inputs to a neuron. The impact of the CRF on firing rate is regulated by a gain control, or normalization signal, that captures the impact of other neural machinery [24]. Mathematically, this can be formulated as:

$$R(i) = M + R_{max}\frac{CRF(i)^n}{\sigma^n + G(i)^n} \qquad \text{Equation (1)}$$

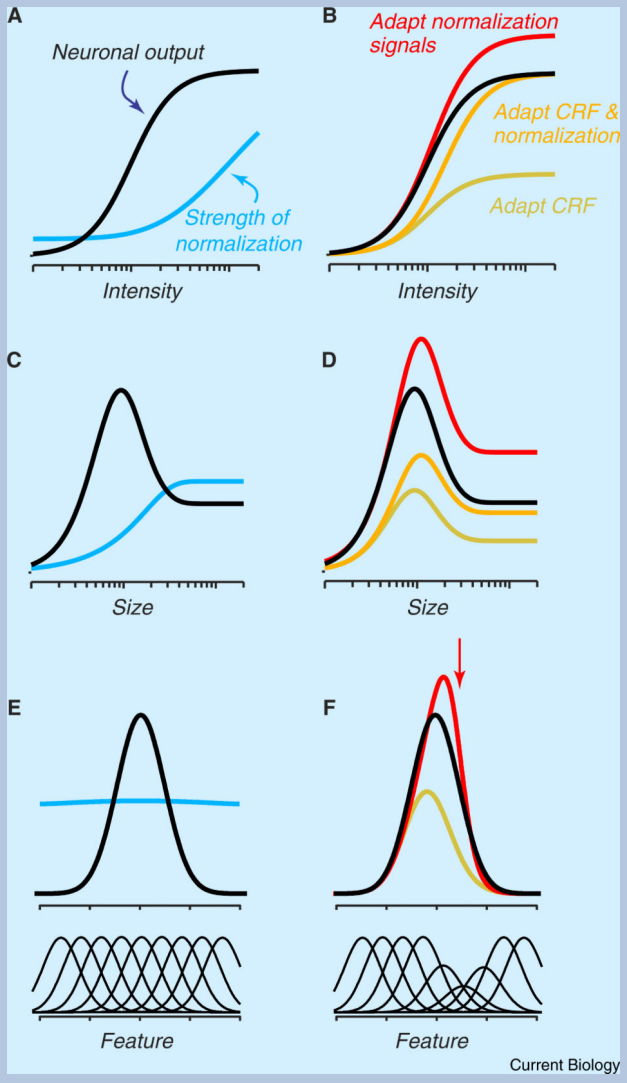
where R is the response of the neuron, i is the intensity of the stimulus, M is the maintained activity in absence of a patterned stimulus, R_{max} the maximal response, and n an exponent that captures the impact of an output nonlinearity. Normalization is captured by this equation because stronger drive to the CRF – the numerator – results in stronger responses; stronger drive to the normalization pool, the denominator G, reduces activity, in a divisive manner. The normalization pool is typically considered to be the summed activity of many neurons, with different stimulus preferences, which are not explicitly defined here. The effective strength of the normalization signal is determined in part by the constant δ.

Panel A in the figure shows the intensity-response function of a typical sensory neuron: response grows with intensity, and then saturates. The blue line in panel A shows how the relative strength of the normalization signal is thought to increase with intensity [24]. Panel B in the figure shows predicted responses of a neuron when adaptation has an impact on the CRF (yellow line), normalization (red line), or both (orange line). If adaptation desensitises only the CRF, it affects responses at all intensities, as if there was a change in “response gain”. A weakening of the normalization signal enhances responses, particularly to stronger stimuli. Finally, if adaptation desensitises the CRF and normalization in a balanced way, it reduces response at low intensities but leaves responses to strong stimuli unaffected, as if there were a change in “contrast gain”. Note that joint adaptation of the CRF and normalization brings about a horizontal shift in the intensity-response function; this shift is a characteristic effect of adaptation and in previous work has been captured by changing s [31,33,34], which has the same impact in Equation (1).

A normalization model can also account for adaptation's effect on spatial tuning [24,38,57]. The black lines in figure panels C and D show the size-tuning function of a typical visual neuron: response first grows with size, reaches a plateau, and then declines. The initial rise primarily reflects summation within the CRF and the subsequent decline is because normalization from the surround is recruited when the stimulus extends beyond the CRF (blue line). Figure panel D shows predicted responses of a neuron when adaptation has an impact on the CRF (yellow line), the surround (red line), or both (orange line). If adaptation desensitisesonly theCRF, it reduces response to all sizes; if adaptation desensitises only surround normalization, response is increased primarily at larger sizes. Note that adaptation can have spatially specific effects in both the CRF and

surround [38]; these can be capturedby supposingthat adaptation desensitises only those parts of each mechanism that are covered by the adaptor.

This simple model is also capable of explaining the diverse effects of adaptation on neural tuning along other stimulus dimensions [11,26,28]. Figure panel E illustrates the tuning of the CRF and normalization of sensory neurons when constructed by appropriately weighing tuned inputs, drawn below the panel. The normalization pooldrawsfrom a wider range ofinputsthanthe CRF.Whenanadaptor desensitises a subset of inputs to the CRF, it reduces response particularly around the adaptor and therefore shifts the preferred stimulus away from the adaptor (figure panel F, yellow); when it has an impact on normalization signals, adaptation can increase response, particularly for stimuli that resemble the adaptor (figure panel F, red).



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Box 2 Impact of adaptation on population activity

It is well known that sensory processing requires populations of neurons. The information encoded by a population depends on the tuning of individual neurons, their response variability, and how activity is coordinated among neurons. The structure of pairwise 'noise' correlations, in particular, may strongly influence population performance [126–128].

Adaptation has been shown to alter correlations, but there is not yet consensus about its effects. In somatosensory cortex of anaesthetised rat, adaptation increases the magnitude of correlations and response variability, particularly for weak stimuli [46,129]. In anaesthetised cat V1, adaptation has little effect on correlations [99]; in awake monkey V1, adaptation may reduce correlations [130].

Other work has sought to understand how adaptation affects finer-temporal correlation, namely gamma-band activity or the synchronisation of spiking responses [131]. Adaptation increases high-frequency oscillatory activity in the locust olfactory system [132] and the visual cortex of primates [133,134]. Similar effects can be observed in MEG measurements from higher stages of human visual cortex [135]. However, other studies have found that adaptation reduces the synchronisation of spiking activity [136,137], and power in gamma and higher frequencies of the local field potential [75,77,138].

Some of the inconsistency across studies may reflect differences between species or sensory areas, or other experimental details. However, a tantalizing possibility is that the inconsistencies may be explained in part by variations in the recruitment of normalization signals. The magnitude of correlations depends strongly on network state and likely on the balance between excitation and inhibition [139]. Similarly high-frequency fluctuations like gamma are thought to reflect the temporal interaction of excitatory-inhibitory circuits, and are stronger for stimulus configurations that recruit normalization signals [138,140]. In this regard, it is worth noting that visual studies have measured adaptation effects on correlations with strong stimuli [99,130], whereas the increase in correlations in the barrel system is observed for weaker stimuli [46]. Thus, it may be important to characterise adaptation effects across a range of stimulus intensities [46], and to consider the behaviour of normalization signals at each intensity.

A final way in which adaptation may alter population coding is by affecting how those responses are 'read out' by downstream areas. In perceptual learning, another form of experience-based plasticity, there is some evidence that behavioural effects involve improved read out [141,142]. To date, adaptation work suggests little change in how adapted responses are interpreted by downstream networks, both because effects cascade through early stages of the visual system and because robust aftereffects suggest an inability of higher cortex to fully correct for perturbed sensory representations. Nevertheless, read out may be adjusted when an adaptation state is experienced repeatedly [143]. In addition, when adaptation weakens inhibition, it may alter the

temporal window in which feedforward signals are summed by downstream networks [136,144], altering their sensitivity to coordinated input.

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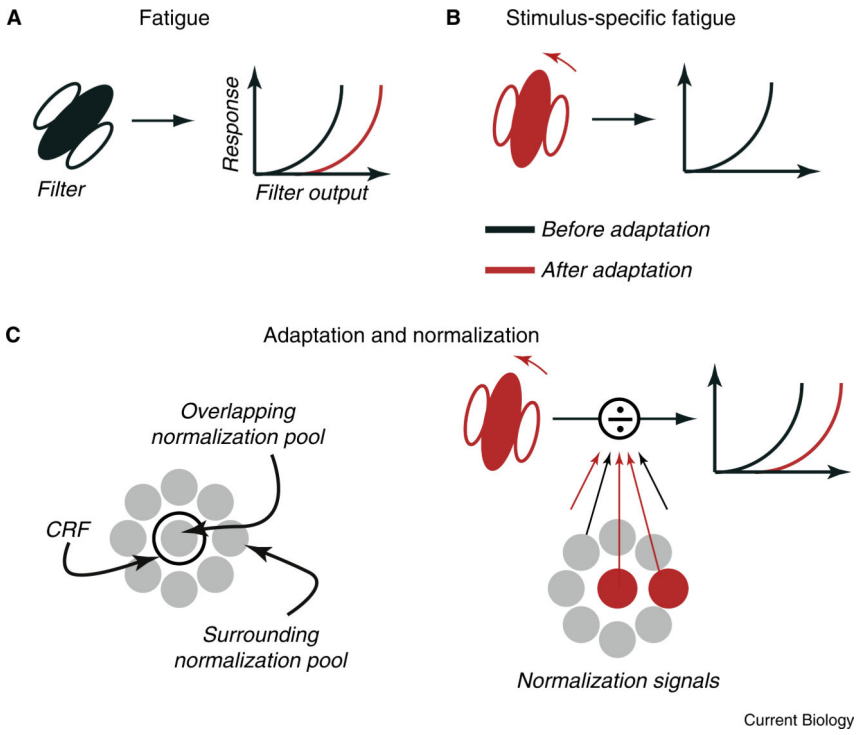

Figure 1. Frameworks of adaptation

(A) Fatigue: simple models of sensory response include a linear stage, which captures the weighted summation of synaptic inputs and dictates the shape of tuning curves, and a non-linear stage that transforms this weighted sum into an output. Fatigue is captured by a change in the non-linear function that generates outputs, causing all subsequent responses to be reduced. Here and elsewhere the red indicates sites and effects after adaptation; black indicates before adaptation. (B) Stimulus-specific fatigue: fatigue is generated in a subset of synaptic inputs to the neuron under study and therefore deforms the linear filter of the CRF. The impact of adaptation is greatest for subsequent tests that resemble the adaptor, often generating “repulsive” shifts in tuning curves. (C) Normalization models interpose a gain control between the filter output and non-linearity. This gain control draws on a large pool of signals that cover the CRF and extend beyond it. Their suppressive impact is captured by a divisive interaction with the CRF. In this framework, adaptation can have independent impact on the CRF and normalization signals.

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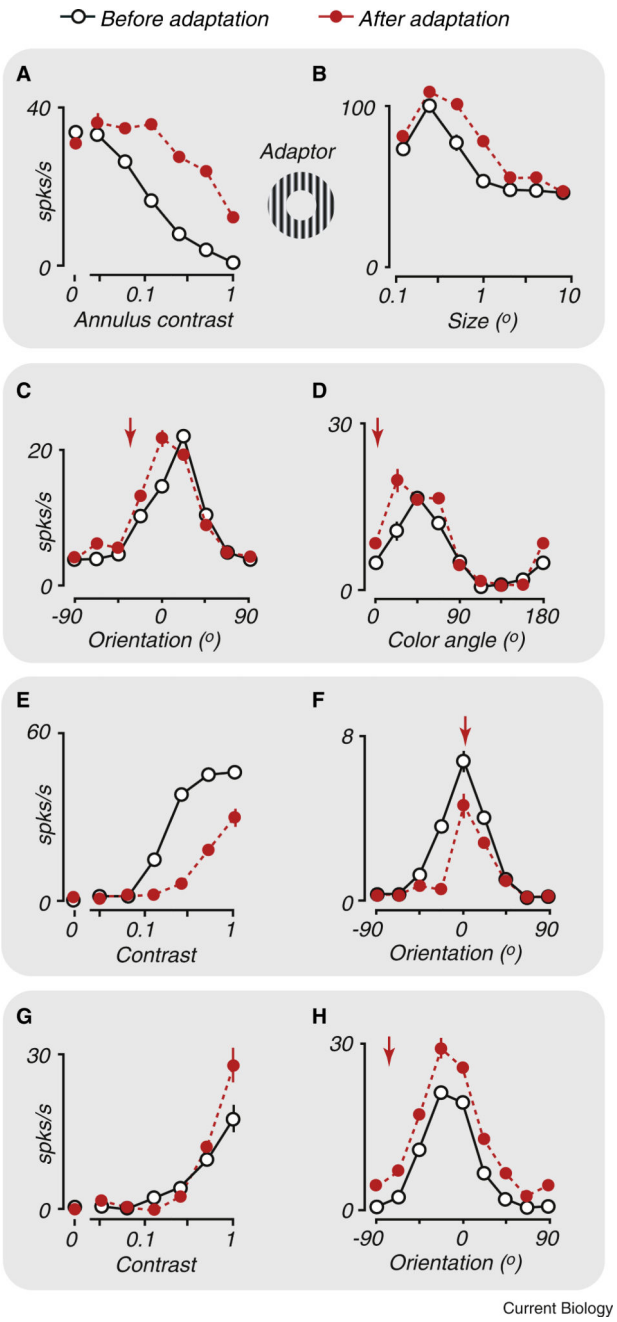

Figure 2. Impact of adaptation on visual sensory neurons

Each panel compares response before (open symbols) and after (red filled symbols) prolonged adaptation to a high contrast stimulus. Arrows indicate the identity of the adapting stimulus when measuring tuning curves. (A,B) Adaptation to annular stimuli can enhance responsivity and change spatial summation. (A) Response of a V1 neuron to a stimulus within the CRF is suppressed by contrast in a surrounding annulus. Adaptation confined to the annular region weakens this suppression, facilitating responses to large stimuli. (B) Responses of an LGN neuron to stimuli of increasing size, illustrating a 'suppressive surround' that reduces response to large gratings. After adaptation to an annular

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grating, the sensitivity of the surround is reduced, increasing the effective summation area of the neuron. (C,D) Adaptation to a stimulus can attract tuning curves towards the adaptor. (C) Responses of V1 neurons to orientations that are similar to the adapting stimulus are facilitated, with little effect on response to other orientations. (D) Same as (C), but for color. (E,F) Adaptation effects include reduced responsivity. (E) Contrast-response function of a V1 neuron for a stimulus in its preferred orientation. Adaptation with the preferred stimulus shifts the contrast-response curve to the right. (F) Orientation tuning curve of a V1 neuron. Adaptation leads to weaker responses for most orientations. (G,H) Adaptation to a non-preferred stimulus can lead to response facilitation. Response of V1 neurons after adaptation to gratings orthogonal to the preferred orientation. (G) Adaptation can increase response to subsequent high contrast tests of the preferred orientation. (H) Response is increased across a wide range of stimuli, suggesting that adaptation has desensitised a broadly tuned normalization signal. (A) Redrawn from [25]. (B) Redrawn from [38]. (C) Redrawn from [26]. (D) Redrawn from [28]. (E) Redrawn from [31]. (F) Redrawn from [26]. (G) Redrawn from [31]. (H) Redrawn from [26].

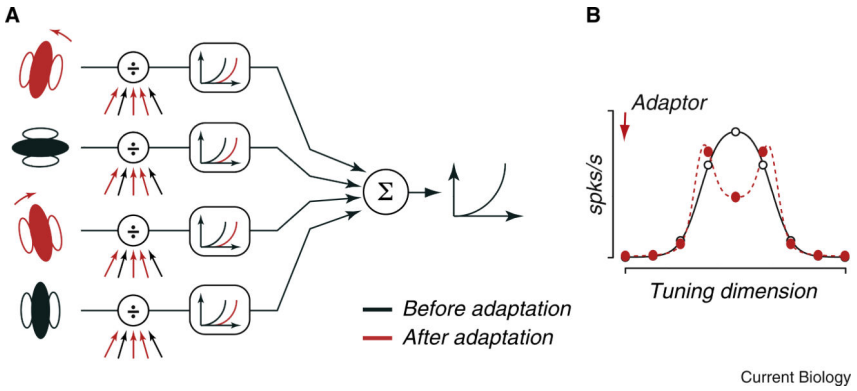

Figure 3. Cascading of adaptation in sensory pathways

(A) Schematic of a generic, hierarchical sensory pathway. The outputs of neurons at earlier stages of processing are weighted and summed, and transformed into spiking activity. The higher order neuron is unaware of adaptation effects earlier in the pathway (red symbols). (B) Neural tuning of the higher-order neuron (open symbols), conferred by the weights it applied to neurons at earlier stages. Absent compensation for adaptation effects at earlier stages, tuning may be distorted by adaptation (red filled symbols), derailing the computations the higher-order neurons perform. Redrawn from [73].

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