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Adaptation: from single cells to BOLD signals

Bart Krekelberg[1], Geoffrey M. Boynton[2] and Richard J.A. van Wezel[3]

[1]Rutgers University, Center for Molecular and Behavioral Neuroscience, 197 University Avenue, Newark, NJ 07102, USA
[2]The Salk Institute for Biological Studies, Systems Neurobiology Laboratories, 10010 North Torrey Pines Road, La Jolla, CA 92037, USA
[3]Utrecht University, Helmholtz Institute, Padualaan 8, 3584 CH, Utrecht, The Netherlands

Functional magnetic resonance imaging adaptation (fMRIa) is an increasingly popular method that aims to provide insight into the functional properties of subpopulations of neurons within an imaging voxel. The technique relies on the assumption that neural adaptation reduces activity when two successive stimuli activate the same subpopulation but not when they stimulate different subpopulations. Here, we assess the validity of fMRIa by comparing single-cell recordings with functional imaging of orientation, motion and face processing. We find that fMRIa provides novel insight into neural representations in the human brain. However, network responses in general and adaptation in particular are more complex than is often assumed, and an unequivocal interpretation of fMRIa results can be achieved only with great care.

Adaptation

A long tradition in studies of human perception has shown that prolonged exposure to orientation, motion or faces causes significant changes in perception. For example, viewing an oriented line for a long time causes subsequent lines to appear tilted away from the adapting orientation [1,2]. In the motion domain, a striking illusion occurs when one looks first at a moving pattern for several seconds and then at a stationary pattern. The stationary test pattern is perceived to move in the direction opposite to that of the moving stimulus – the motion after-effect [3]. An analogous face after-effect has recently been reported: after viewing male faces, subsequent faces look more female [4]. These perceptual phenomena show that something in the brain must change with prolonged exposure. Functional magnetic resonance imaging adaptation (fMRIa; Figure 1) follows a long line of adaptation research in human psychophysics [5,6] and aims to exploit those changes to gain insight into the neural representations underlying these percepts [7].

The wealth of data from both imaging and single-cell studies of adaptation in these three domains means that results can be compared across the two methods. This article is not meant to be an exhaustive review of the fields; instead, we focus on recent studies that enable us to validate fMRIa. We refer to the recent literature for general reviews of analysis of orientation [2,8], motion [3,9] and faces [10,11]. We also focus on the changes in neural and blood-oxygen-level dependent (BOLD) responses that occur with short lags between repeated stimuli, and do not discuss the long-lag repetition suppression that has been linked to phenomena such as priming [12]. Finally, we do not discuss to what extent BOLD signals are a direct reflection of neural spiking responses or synaptic activity, but simply assume that the BOLD signal provides a general measure of neural 'activity'. Readers interested in the relationship between electrophysiological and imaging measures of neural activity can consult recent reviews [13,14].

Orientation

In the first study to use adaptation with fMRI, Tootell *et al.* [15] measured BOLD responses when gratings, presented for 40 s at a time, switched from one orientation to another. They found that in the primary visual cortical area V1, the largest responses occurred when the gratings switched to an orthogonal orientation. For smaller orientation changes, the response was progressively smaller. This suggests that the new orientations excited fresh subpopulations of neurons, and that the amplitude of the response reflects the orientation-tuning properties of the underlying neurons in V1.

Three recent studies [16–18] have replicated and extended this result. These studies used a so-called top-up long-term adaptation design. Subjects viewed an oriented grating for a long time (at least 20 s) before scanning started. During scanning, brief (top-up) presentations of the adapting orientation appeared interleaved with brief presentations of a test pattern of a different orientation. In all three studies, a probe orthogonal to the adapting stimulus evoked the strongest responses in early retinotopic visual areas, including V1. Fang *et al.* [17] additionally showed that the BOLD response increased as the angle of the probe stimuli differed more from the angle of the adapting stimulus.

These results are consistent with similar electrophysiological studies showing orientation-selective adaptation in macaque V1 after prolonged exposure (>10 s) [19,20]. Hence, these studies support the view that fMRIa can reveal the tuning properties of orientation-selective

Corresponding author: Krekelberg, B. (bart@rutgers.edu).

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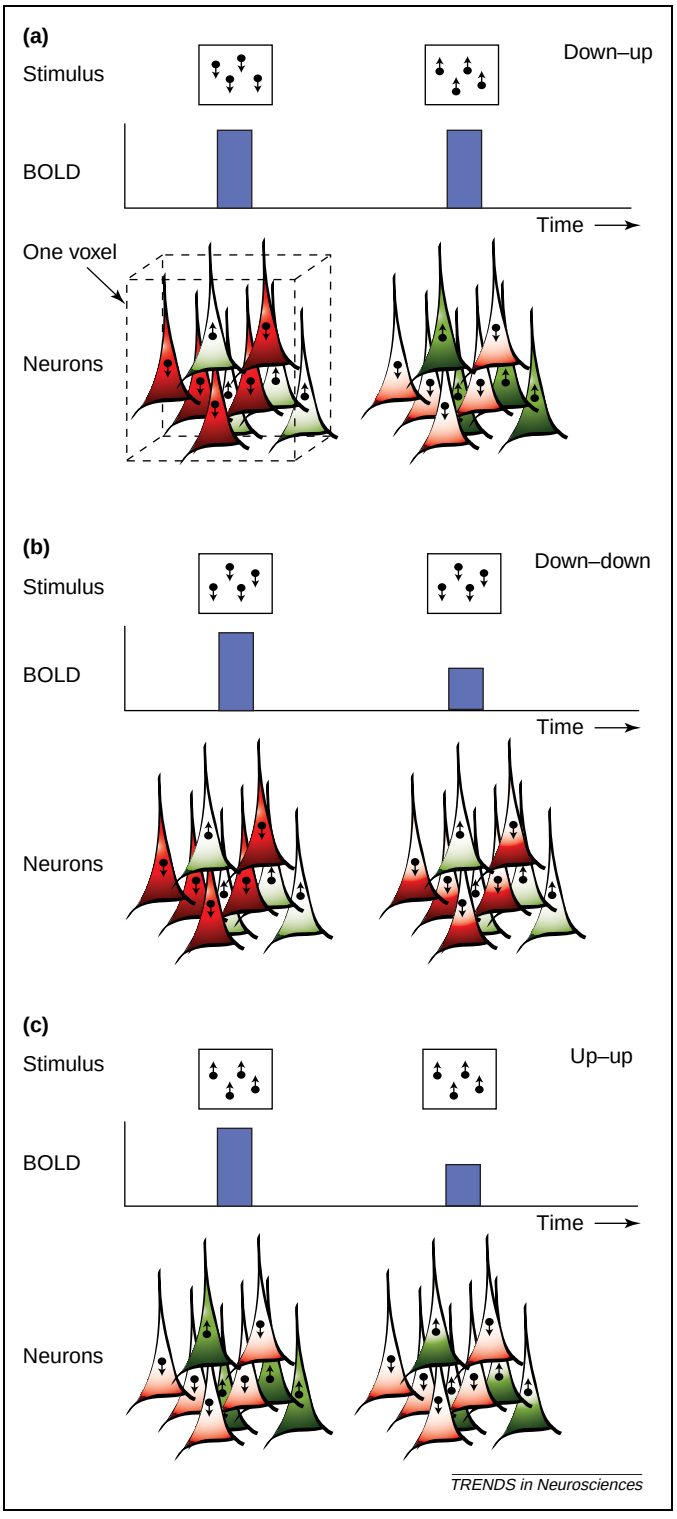

Figure 1. The principle of functional imaging adaptation. Assume that a particular imaging voxel contains two cell populations, with the same number of cells in each population. For simplicity, assume that one population responds to downward motion (red neurons; downward arrows) and the other to upwards motion (green neurons; upward arrows), although the logic of the approach applies to any two stimulus categories. The blood-oxygen-level dependent (BOLD) signal reflects the summed activity of both populations. Consequently, the standard block design that alternates downward and upward stimuli shows no modulation in the signal **(a)**. The correct conclusion to draw from such a finding is that there is no spatial organization of up-preferring or down-preferring neurons at the scale of the imaging voxels. As this example shows, it is incorrect to conclude that there are no cells in the imaging voxel that selectively respond to up or down. **(b)** In a typical functional magnetic resonance imaging (fMRIa) paradigm, the downward stimulus is repeated. The first presentation evokes a large response in the neurons and hence a large BOLD signal but, owing to neural adaptation, the second presentation evokes a smaller neural response (indicated by lighter shading of the red neurons) and hence a smaller BOLD response. This response contrasts with the condition of alternating up and down stimuli. If the stimuli activate separate populations, the adaptation in the up-population does not affect the response in the down-population (a) and the total response should be higher ('release from adaptation') than if the same population is stimulated twice. However, lacking other information, the observation that down–down stimulus pairings generate smaller BOLD signals than up–down pairings might simply reflect the fact that the area being studied does not respond to downward motion at all. To exclude this possibility, the response to the repeated presentation of the up stimulus is measured **(c)**. If both down–down and up–up presentations generate smaller BOLD responses than do up–down presentations, then a nonlinear mechanism must reduce the BOLD response when the same stimulus is presented twice. Assuming that stimulus-selective neural adaptation is the underlying nonlinear mechanism, one can conclude that the voxel of interest contains separate subpopulations selective for up and for down stimuli.

neurons in cortical areas that are early in the visual pathway.

Other fMRIa studies, when taken at face value, seem to suggest that V1 does not contain neurons selective for orientation or even spatial position. For instance, presenting the same face multiple times leads to adaptation in the fusiform face area [7] (see the section on Faces, later in this review) and release from adaptation occurs when pictures of the same face from different viewpoints are shown [21]. However, these stimulus manipulations did not cause any differential activation in V1 [22]. This is mysterious because the global stimulus manipulation (viewpoint change) includes local changes in orientation and position that, because V1 contains orientation-selective and position-selective neurons, should cause release from adaptation. Recent fMRI studies suggest that these discrepancies arise because (i) higher areas in the visual processing stream might adapt more easily than lower areas, and (ii) the amount of adaptation in any given area depends on the timescale of stimulus presentation. The next section reviews the complexity of orientation adaptation effects when one considers shorter timescales.

Timescales of adaptation

Boynton and Finney [23] adapted their subjects using one-second presentations of a full-field grating, followed by at least 1.25 s presentation of a blank screen, and then presentation of a test grating at an orientation identical or orthogonal to that of the first grating. At this intermediate adaptation timescale, they found no orientation-specific adaptation in either V1 or V2. However, the amount of adaptation increased along the hierarchy of visual cortical areas (i.e. V3 and V4v). Fang *et al.* [17] removed the 1.25 s blank period from the design and replicated these findings; this shows that the absence of adaptation in V1 was not due to rapid recovery between the adaptation and the test stimulus. Moreover, they confirmed the importance of the timescale by showing that identical stimuli in a long-term adaptation design did evoke significant adaptation in V1.

Kourtzi and colleagues [24–26] used even shorter stimulus durations: typically an adapting stimulus of 300 ms, followed by a 100 ms blank interval and then a 300 ms test stimulus with the same or different orientation as the adapting stimulus. This design evoked significant adaptation in all early areas of the visual cortical pathway, including V1. Moreover, when small

oriented elements were organized to form a global pattern, pattern-selective adaptation was found in both the lateral occipital complex and V1. Hence, at these short timescales, there was no conflict between pattern-selective adaptation at global and local levels, or between areas along the visual hierarchy [24,26].

One possible explanation for these findings is that the short stimulus durations tap into neural mechanisms of transient versus sustained responses. Typically, many V1 neurons respond with a brief transient burst of activity followed by a lower sustained rate of firing; single-cell studies in macaque V1 show that this process is stimulus selective [27,28]. By contrast, in designs using stimuli of 1 s duration, the BOLD signal should mainly reflect the (longer) sustained phase. We know of no studies investigating the stimulus-selective nature of adaptation in single V1 cells at that intermediate timescale. However, in the macaque middle temporal area (MT), adaptation to moving stimuli of 2 s duration does reduce firing [29,30], albeit less than at the typical long-term adaptation timescale of tens of seconds [31].

Together these studies suggest that the timescale of stimulus presentation and the duration of adaptation have a strong influence on the susceptibility of an area to adaptation. This is not a big issue in an experiment with a positive result: if the data show selective adaptation, then the timescale must have been chosen appropriately. The problem lies with the interpretation of null results: the absence of adaptation cannot simply be taken to mean that the underlying neuronal populations are not selective for the chosen stimulus.

Motion

Visual motion information in the brains of humans and monkeys is processed by a distributed network of largely similar cortical regions, although there are some differences between species [32–34]. Neurons in these areas are direction selective; they respond vigorously to a stimulus moving in one direction (the preferred direction) but much less to motion in the opposite direction. A stimulus in this so-called anti-preferred direction can even reduce the response of the neuron below the spontaneous firing rate.

When direction-selective neurons are stimulated in their preferred direction, the response to a subsequent preferred stimulus is decreased. The percentage decrease in activity depends on stimulus duration and the time between adaptation and test, but generally the reduction is ~20–30% [29–31,35–38]. These results are in line with fMRIa studies that show the BOLD response to a stimulus in one motion direction to be attenuated when it follows a stimulus in a similar motion direction [26,39–41]. This summary of motion adaptation supports the basic assumption of fMRIa studies: adaptation reduces the response to subsequent moving stimuli.

However, single-unit studies in MT have revealed more complex properties of neural adaptation. We now discuss three such findings that complicate the interpretation of fMRIa results: disinhibition, inherited adaptation, and adaptation-induced changes in tuning.

Disinhibition

Motion-sensitive neurons in MT are not isolated feature detectors; they are part of an intricate network that achieves its direction selectivity through complex and nonlinear interactions among neurons with different preferred directions [42,43]. In particular, motion opponency (inhibition between neurons with opposite preferred directions) is thought to underlie the response of this network. In such a network, adaptation of one neuron can reduce the inhibitory input to other neurons and thereby increase their response.

When an MT cell has been adapted using a stimulus moving in the anti-preferred direction and strictly within the classical receptive field of the cell, the ability of the cell to respond to a stimulus in the preferred direction can be either enhanced or suppressed, but on average only minor changes are observed [29,31,36–38]. However, one early study reported a strong enhancement in the response to the preferred direction after adaptation to a large pattern moving in the null direction [44]. In this study, the adaptation stimulus might have stimulated the inhibitory surround of the cell; hence, the enhancement might have been due to disinhibition. The extent of disinhibition is expected to depend closely on the properties of the network.

Human imaging studies typically use large stimuli and, because the BOLD signal reflects the activity of many cells, these studies inevitably involve adaptation of both the classical receptive field and the inhibitory surround of many cells. Consistent with the proposed influence of disinhibition, imaging studies report an increase in the BOLD response of human area MT+ (hMT+) to a stationary stimulus following adaptation to a single direction [45–48]. Although other studies suggest that these hMT+ BOLD increases are confounded by attentional effects [40], the logic of the argument applies generally. Thus, even when single cells in a typical physiology experiment reduce their response after adaptation, disinhibition can in principle result in an overall increase in the network response.

Inherited adaptation

There is no disagreement that adaptation changes the neural response in MT. One can question, however, whether the adaptation originates in MT or is 'inherited' from areas earlier in the visual pathway. Kohn and Movshon [31] showed that long-term adaptation using a small pattern at one location inside the receptive field of a neuron did not affect sensitivity of the neuron to a test pattern presented at another location inside the receptive field. This suggests that the adaptation took place in units with much smaller receptive fields, presumably in V1 (the major source of input for MT). Consequently, adaptation effects observable at the level of one cortical area (in this case MT) can be inherited from earlier levels (V1).

Priebe *et al.* [37] investigated the adaptation of single MT cells on a short (~100 ms) timescale. Contrary to Kohn and Movshon's findings, they observed that short-term adaptation anywhere inside and even to some extent outside the MT receptive field affected the subsequent response to a stimulus within the receptive field. This

implies that the short-term adaptation took place in units that have receptive fields larger than that of the typical MT cell. Priebe *et al.* proposed that this 'unit' is the intracortical circuit in MT.

fMRIa studies interpret the existence of stimulus-selective adaptation effects in an area as evidence for selective processing in that area. If data show that there are no adaptation effects in upstream areas under the same circumstances, that conclusion seems reasonable. However, if such information is not available, a firm conclusion cannot be drawn. The single-cell studies clearly show that (i) the presence of adaptation effects does not uniquely specify the locus of adaptation [31], and (ii) adaptation at different timescales might take place in different functional units [31,37]. Future fMRIa studies in which adaptation is observed in both early and late areas of the visual pathway could use some of the techniques that psychophysicists and electrophysiologists have developed to pinpoint the location of adaptation and to disentangle inherited from intrinsic adaptation. For instance, as we have already discussed, the scale of spatial transfer of an adaptation effect might indicate which cortical areas are involved.

Adaptation changes tuning

The largest adaptation effects typically occur when an adaptation stimulus evokes a strong response from a cell. This fits with a view of adaptation as a passive process of neural fatigue: the more a neuron fires, the more its subsequent response is reduced [29]. When describing adaptation as fatigue, the role of the test stimulus is ignored – the test stimulus is considered a neutral probe to measure the effectiveness of the adaptation. However, two recent studies have revealed important interactions between adaptation and test stimuli in MT that are inconsistent with this view.

Kohn and Movshon [36] showed that following any given adaptation direction, the adaptation effects were smallest for test directions equal to the adaptation direction. Krekelberg *et al.* [30] reported a similar finding for speed adaptation: adaptation effects were smallest when tested at the adaptation speed and increased with the speed difference between the adaptation and test stimulus. This implies that adaptation in MT does not simply reduce firing, but changes the tuning curves for both direction and speed. These changes might underlie the perceptual improvement in direction and speed discrimination that occur with adaptation [30,36].

It is important to stress that these data should not lead to rejection of the fundamental assumption behind fMRIa – that stimuli to which a cell responds strongly induce strong adaptation effects. In other words, adaptation can be used to infer that a subpopulation of neurons responds to the stimulus. However, these data show that when cells are given a stimulus to which they respond strongly, the amount of adaptation recorded depends on the subsequently presented test stimulus. In other words, there is an interaction between the adapting stimulus and the test stimulus. fMRIa studies need to take this possible interaction into account. Interactions between adaptation and test stimuli have recently also been demonstrated forcefully in an explicit test of fMRIa as a method to infer object selectivity in the inferotemporal cortex of the macaque [49]. These interactions, and the fact that there seem to be fundamental differences in these interactions even between areas early in the visual pathway, such as V1 and MT [20,36], complicate the interpretation of adaptation results. In particular, such interactions prevent a straightforward deduction of neuronal tuning width from fMRIa data alone.

Faces

Three human cortical areas consistently respond more strongly to pictures of faces than to pictures of objects: the fusiform gyrus (hFG), the inferior occipital gyrus (hIOG) and the superior temporal sulcus (hSTS) [50]. Recent functional imaging studies in macaques have also revealed consistent patches in the anterior parts of the superior temporal sulcus (aSTS) and the inferior temporal gyrus (IT) that were activated more when the animals viewed faces than when they viewed objects [51,52].

Adaptation paradigms have been used extensively to answer questions about the nature of the neural representation of faces [7]. Because humans can recognize the identity of a person from many different pictures of a face, one important issue is whether face areas contain an invariant representation. Andrews and Ewbank [21] investigated this by presenting either a set of different face images or the same face image multiple times. Multiple presentations of the same face led to a reduction in response from the hFG; this reduction was also observed when the repeated images had different sizes. This suggests that the adaptation was not due to low-level physical properties, but to a size-invariant representation of the identity of the face. However, the adaptation disappeared for the presentation of pictures of a single face taken from different viewpoints. This indicates that the representation in hFG is not viewpoint-invariant and mirrors findings in macaque aSTS, where single cells are face-preferring but not viewpoint-invariant [53–55]. These fMRIa results provide important insight into human face processing, and the single-cell data support them. However, some findings cast doubt on the general applicability of the adaptation paradigm.

Response enhancements

Even though many single cells show suppression of responses to repetition, some show enhancement. In a recent study, for instance, responses to repetition were suppressed, enhanced or unaffected in approximately equal proportions in macaque IT [54]. Functional imaging studies show a similarly mixed range of effects across areas. Zago *et al.* [56] demonstrated repetition suppression for everyday objects in most ventral areas, but several parietal and occipital areas showed significant repetition enhancement.

Additional processing

Even in the aforementioned study by Andrews and Ewbank [21], repeated presentation of pictures of a face taken from different viewpoints and with different expressions increased the BOLD signal in the hSTS. The

authors interpreted this as the result of additional processing performed by the hSTS to analyze changeable aspects (such as expressions) of the same face.

This interpretation seems reasonable but, if additional processing takes place in the hSTS for repeated images, then it is at least possible that it also takes place in other areas, such as the hFG. In other words, any response should be interpreted as a mixture of (unknown) additional processing and adaptation. This complicates the interpretation of the absence of repetition suppression in the hFG for viewpoint-variant faces. The hFG might adapt even during viewpoint changes but, because additional processing takes place, its BOLD signal shows no overall reduction. This demonstrates the importance of designing experiments that limit additional processing as much as possible.

Limiting additional processing

Designs that might limit additional processing include those in which only two images are presented in rapid succession (<1 s) or where stimuli are followed by masks. Winston *et al.* [57] used such a design and revisited the representation of face identity and facial expressions. They found suppression following repetition of faces with the same identity but different expressions in the hFG, confirming the aforementioned results [21]. However, in this paradigm, faces with the same expression but different identities led to suppression in the hSTS. This suggests that the hFG contains an expression-invariant representation of the identity of a face, whereas the hSTS contains an identity-invariant representation of expression.

Face detectors?

Single-cell responses in the IT cortex are not proportional to the match between a cell and its preferred face but, rather, are a signal that varies with time and depends on identity, expression [58,59] and the action that precedes it [60]. Moreover, human imaging data show that face information is available outside areas that respond most when faces are present [61]. This indicates that the neural code for faces is distributed [62] and not a simple 'thermometer code' in which the BOLD signal is proportional to the match between a face and some internal representation of that face. Taken together with the repetition enhancement and additional processing we have already discussed, this shows that these regions are not passive face detectors whose response fatigues with stimulus repetition. As the next section will show, however, it is possible to design a stimulus set for which the BOLD response looks strikingly like the output of a simple feature detector that exhibits fatigue with repeated stimulation.

Constructing a feature detector

Building on previous behavioral work [63] Loffler *et al.* [64] designed such a stimulus set for the representation of faces in the hFG. They first determined a high-dimensional vector to describe any given face on the basis of a set of salient features in a face image (e.g. position of the eyes or position of the hairline). Next, they determined the average face vector over a large number of subjects. The parameters they chose to describe an arbitrary face were the 'distance' and 'direction' (in the high-dimensional face space) away from this mean face. In a functional imaging experiment, they then showed that the response of the hFG increased sigmoidally when faces with increasing distance to the mean face were presented. Phrased in our terms, this shows that the BOLD response in the hFG is well described as a detector of mean face distance. Loffler *et al.* went on to show that different faces with the same mean face distance but different face directions led to little adaptation, suggesting that different subpopulations respond to faces lying in different directions in this face space. Finally, they showed faces with the same face direction but different mean face distances. This led to nearly as much adaptation as presenting the same face repetitively, suggesting that cells in the hFG respond to a wide range of faces that lie in the same direction in face space. This study shows the promise of fMRIa: it can reveal not only where but also how information is represented in the human brain.

Concluding remarks

The data reviewed here show both the promise and the possible pitfalls of using fMRIa to study the visual system. The promise is that one might resolve functional neural organization beyond what standard imaging techniques can achieve and obtain insight into the neural representation of information. Given its noninvasive nature, this technique can be applied to understanding the human brain.

The pitfalls are caused by the complexity of the same neural processes that we are trying to understand. For example, stimulus repetition can cause neural response changes at one timescale but do little at another timescale. Stimulus repetition can lead to changes at early levels of the visual system that percolate upwards, it can change the dynamics of neural processing, causing disinhibition and altering tuning, or it might trigger additional neural processes that cause changes in activation. Although we have illustrated these possible pitfalls with examples from processing of information on orientation, motion, and faces, we believe that many of these issues generalize at least in principle to the interpretation of all fMRIa results. With careful experimental design, some of these difficulties can be avoided, but a better understanding of adaptation at the single-cell level – which is interesting in its own right – could greatly improve our ability to interpret fMRIa data. However, extrapolating the adaptation properties of a whole area from a sample of at best a few hundred single cells is not to be taken lightly. Quantitative imaging studies that measure adaptation in paradigms that closely match those of single-cell studies are required to bridge this gap.

Finally, the BOLD signal is only an indirect measure of neural activity [14], and neurovascular coupling includes many nonlinear processes [65,66]. This implies that the weaker fMRI response to longer-lasting stimuli [67] or to successive stimuli [68], which fMRI-adaptation attributes to neuronal adaptation, might be caused by nonlinearities in the neurovascular coupling process. An interesting

speculation therefore is that fMRI-adaptation works because it takes advantage of nonlinearities in the hemodynamic coupling process, and not because of neuronal adaptation. That is, the fMRI response might show a release from adaptation because the novel stimulus excites a subpopulation of neurons that has a different, fresh vascular supply. Such a mechanism would allow fMRI-adaptation without neuronal adaptation. Moreover, nonlinear neurovascular coupling complicates quantitative interpretation of a BOLD signal reduction in terms of neural selectivity. Thus, even if all neurons were identical feature detectors, 50% adaptation would not imply that 50% of the neurons were selective. Such quantitative information might be available in the detailed shape of the BOLD signal. Changes in the initial dip and the post-stimulus undershoot, for instance, might reflect the number of activated cells [69]. Here too, studies that combine imaging with single-cell data could not only provide a better understanding of the underlying mechanisms but also create new tools for studying neural information processing in humans.

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