Selectivity of Neuronal Adaptation Does Not Match Response Selectivity: A Single-Cell Study of the fMRI Adaptation Paradigm

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Summary

fMRI-based adaptation paradigms (fMR-A) have been used to infer neuronal stimulus selectivities in humans. Inferring neuronal selectivities from fMR-A, however, requires an understanding of the relationship between the stimulus selectivity of neuronal adaptation and responses. We studied this relationship by recording single cells in macaque inferior temporal (IT) cortex, an area that shows fMRI adaptation. Repetition of identical object images reduced the responsiveness of single IT neurons. Presentation of an image to which the neuron was unresponsive did not alter the response to a subsequent image that activated the neuron. Successive presentation of two different images to which the neuron responded similarly produced adaptation, but less so than the repeated presentation of an image. The neuronal adaptation at the single-cell level showed a greater degree of stimulus selectivity than the responses. This complicates the interpretation of fMR-A paradigms when inferring neuronal selectivity.

Introduction

Microelectrode recordings of extracellular action potentials have provided crucial information regarding the tuning properties of single cortical neurons, e.g., the orientation (e.g., Hubel and Wiesel, 1968; Schiller et al., 1976) and shape tuning (e.g., Gross et al., 1972; Tanaka et al., 1991) of macaque V1 and inferior temporal (IT) neurons, respectively. The invasiveness of the single-cell recording technique precludes its routine use in humans. Recently, functional magnetic resonance adaptation (fMR-A; Grill-Spector and Malach, 2001; Nacache and Dehaene, 2001) has been used to infer the average tuning or selectivity of neuronal populations in humans (e.g., Tootell et al., 1998; Grill Spector et al., 1999; Kourtzi and Kanwisher, 2000; James et al., 2002; Vuilleumier et al., 2002; Boynton and Finney, 2003; Epstein et al., 2003; Piazza et al., 2004). Although various fMR-A paradigms have been used, their underlying logic is the same: repetition of a stimulus (e.g., A-A) produces reduced activation of neurons responsive to that stimulus, i.e., adaptation. When different stimuli are presented in succession (e.g., B-A), then the degree of cross-adaptation is presumed to reflect the tuning of the neurons. To take the two extremes, cross-adaptation equal to the adaptation obtained by repeating a stimulus would indicate that the same pool of neurons responds equally to the two stimuli (no selectivity), while absence of any cross-adaptation would indicate that different populations of neurons respond to the two stimuli (selectivity). Intermediate levels of cross-adaptation supposedly reflect the degree to which the pool of neurons is tuned to the parameter (Piazza et al., 2004).

Inferring neuronal tunings from fMR-A depends on several key assumptions. One pertains to the exact relationship between fMRI adaptation and neuronal adaptation in a particular brain region, which itself depends on the relationship between fMRI signals and action potentials. The latter is a topic of intense current research (Logothetis et al., 2001; Kim et al., 2004; Logothetis and Wandell, 2004; Mukamel et al., 2005; Niessing et al., 2005). Even if it were accepted that the MR signal reflects neuronal activity perfectly, a second assumption remains that is as critical as the first. This second assumption concerns the relationship between neuronal tuning and neuronal adaptation: one assumes that the same tuning function underlies both the degree of adaptation and the responsiveness of neurons. A simple model (Piazza et al., 2004) relating neuronal tuning and adaptation assumes that a neuron adapts in direct proportion to how well it responds to the adapting stimulus. Consider a neuron that responds to stimuli A and B, but not to C, and three stimulus presentation sequences: A-A, B-A, and C-A. Neuronal adaptation should then occur in the B-A and A-A sequence but not the C-A sequence, and the stimulus selectivity of the adaptation will reflect the stimulus selectivity of the neuron, i.e., the responses to A, B, and C presented as the first stimuli in the sequence. The aim of the present study was to test whether the stimulus selectivity of adaptation matches the stimulus selectivity of a neuron, using single-cell recording in alert macaque monkeys.

We recorded extracellular action potentials from single neurons in macaque IT, a ventral stream area that is known to show neuronal adaptation (Gross et al., 1967, 1969; Baylis and Rolls, 1987; Miller et al., 1991a, 1991b; Riches et al., 1991; Sobotka and Ringo, 1993). Recently, we have shown that macaque IT also shows fMRI adaptation (Sawamura et al., 2005), which makes this region an excellent candidate for examining the relationship between neuronal adaptation and stimulus selectivity. Furthermore, using the same shape stimuli, paradigm, and behavioral tasks, we have shown that the degree of fMRI adaptation in macaque IT is very similar to that obtained in the human lateral occipital complex, a frequent target of fMR-A experiments. One of the two animals of the present single-cell study participated in the previous fMRI study, thus ensuring that the single-cell recordings were made in the region showing fMRI adaptation in that animal.

We employed two different adaptation paradigms, using shape stimuli that were familiar to the animal. In both paradigms, we measured the response to a stimulus, A, to which the neuron responded well, as a function of a previous stimulus that was either the same (A) or

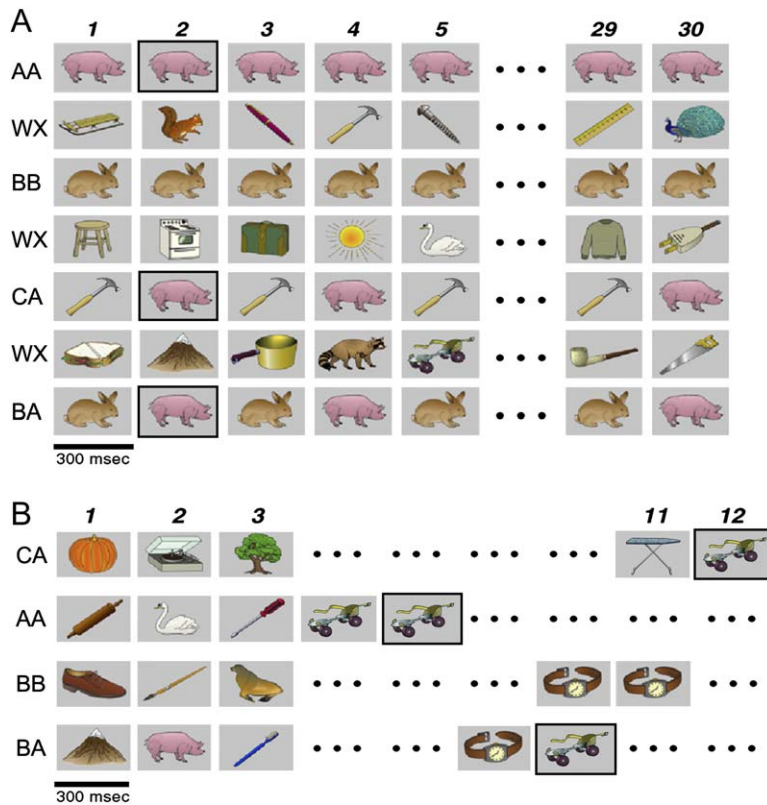*Correspondence: rufin.vogels@med.kuleuven.be

Figure 1. Adaptation Tests

(A) Adaptation test 1. Each row illustrates one of the five possible stimulus sequences. Up to 30 images of objects were presented in each sequence. Stimulus duration and inter-stimulus interval were 300 ms. AA and BB, repetition of images (A and B) that drove the neuron well; BA, alternation of stimuli A and B; CA, alternation of A with C, which was an image that drove the neuron only weakly or not at all. WX sequences consisted of a random sample of 30 images (excluding A and B), newly drawn on each trial sequence. The WX sequences were shown in between the other sequences.

(B) Adaptation test 2. Two images were shown successively, either a repetition of two images that drove the neuron well (AA; BB), or A following B (BA) or C (CA). The latter image was chosen so as not to drive the neuron. The pairs of images were presented in sequences of 12 images and occurred after at least three presentations of other images. The other images of the sequences were randomly drawn on each trial. The same image (A) was shown in the second presentation of the AA, BA, and CA sequences, as indicated by the square.

different (B or C). Because stimuli B and C were chosen to differ in the degree to which they drove the neuron, we could relate the reduction in the response to A, i.e., adaptation, to the responses of the (adapting) stimuli A, B, and C and thus to the stimulus selectivity. The stimulus timing parameters were similar to those used in fMR-A paradigms (e.g., Kourtzi and Kanwisher, 2000).

Results

In a preliminary test, we measured the responses of IT neurons to either 32 color or 32 monochromatic images of drawings of common objects or animals, chosen on a daily basis from stimulus sets of 128 color and 128 monochromatic images. The monochromatic images corresponded to those used previously in a combined human-monkey fMRI study (Sawamura et al., 2005). Because the results were similar for the colored and mono-chromatic images, we will present the data pooled across the two kinds of images. Based on this short initial test, we selected two stimuli, A and B, to which the neuron responded well, and one, C, to which there was little or no response. This was followed by either one of two adaptation tests.

Adaptation Test 1
In the first adaptation paradigm, one of five possible image sequences was presented in a trial (Figure 1A). Each image sequence included up to 30 presentations of object images, the exact number in a given trial (overall mean = 18), depending on the fixation duration of the animal in that trial. Two sequences, A-A- and B-B-, consisted of a repetition of either images A or B, providing

a measure of the adaptation, while in two other sequences, images B or C alternated with A (B-A-, C-A-sequences), providing a measure of the stimulus specificity of adaptation. In order to dis-adapt the neuron, each of these four sequences were followed by the fifth sequence (WX sequence), consisting of up to 30 different randomly selected images (mean = 17), but excluding A and B.

We recorded the responses of 169 responsive single IT neurons in two animals in this first adaptation test, using a stimulus duration and interstimulus interval of 300 ms. As expected, the mean response of this neuronal population decreased when the same stimulus was repeated (A-A-; B-B-; Figure 2). The average reduction in the response was the greatest for the first repetition and decreased for further repetitions. The average degree of adaptation was considerable: median adaptation indices (see Experimental Procedures) for the first and ninth repetition of the A-A- sequence were 0.40 (first quartile, 0.25; third quartile, 0.58) and 0.57 (0.43–0.73), respectively. The mean response to A was significantly larger than the response to B at the first presentation (paired t test; $p < 0.0001$; n =169). The first repetition adaptation indices for A-A- and B-B- were significantly correlated ($r = 0.53$; $p < 0.0001$; n = 169), and the mean within-neuron difference between the adaptation indices for A-A- and B-B- was −0.006 (n = 169), not significantly different from 0.

There was no significant correlation across neurons ($r = 0.002$, n.s.; n = 169) between the first repetition adaptation indices for A-A- and the mean response to the first presentation of A in a sequence. To further examine the correlation of response strength and degree of
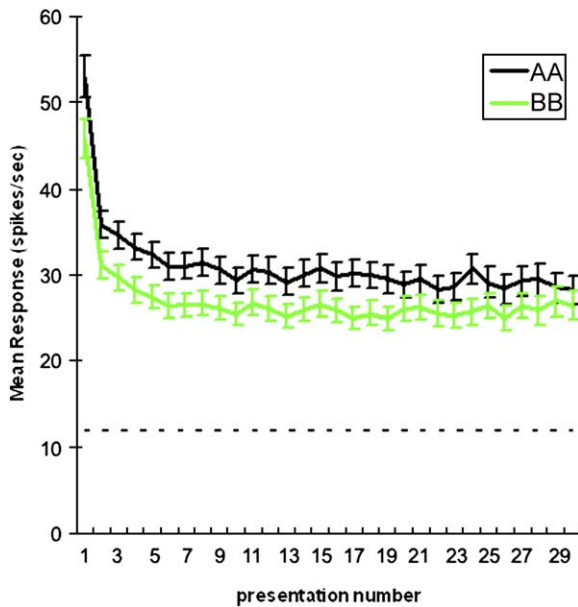
Figure 2. Mean Response of 169 Inferior Temporal Neurons as a Function of the Number of Presentations of the Same Object Image in Adaptation Test 1

Black line, repetition of stimulus A; green line, repetition of stimulus B. Error bars indicate standard errors of the mean. The mean baseline activity is shown by the stippled line.

adaptation, we determined whether two different stimuli, A and B, provide the same degree of adaptation *within* a neuron. For this purpose, we computed for each neuron the percent difference (%RD) between the response to the first presentations of A and B and the percent difference between the first repetition adaptation indices for A-A- and B-B- (%AD_AA-BB; see Experimental Procedures). If the degree of adaptation were to depend on how effective a stimulus is in driving the neurons, one would expect a correlation between %RD and %AD_AA-BB. However, the latter variables showed no significant correlation, neither when examining all neurons (r = −0.05; n.s.; n = 159, removing ten outliers with %AD_AA-BB smaller or larger than 400%), nor when removing outliers by requiring %RD > −100% (r = −0.06; n.s.; n = 157 see Figure S1A in the Supplemental Data available online), nor when taking only neurons with a first repetition adaptation index for A-A- or B-B- larger than 0.33 (r = −0.15; n.s.; n = 129), nor when combining the two requirements (r = −0.16; n.s.; n = 127). This suggests that, at least for IT neurons, the relative degree of adaptation does not depend on how nearly optimal the stimulus is for the neuron. Because the response to A was at least ten spikes per second, we cannot exclude the possibility that for even weaker stimuli, response strength and degree of adaptation might be correlated (Avidan et al., 2002).

The assumption that the degree of adaptation reflects the stimulus selectivity of the neuron can be tested by comparing the response to stimulus A as a second stimulus in the A-A-, B-A-, and C-A- sequences. Images B and A were chosen to drive the neuron, while C was selected so that it did not. If A and B activate the neurons to a similar degree, one would expect a similar reduction in response to A whether it follows A (A-A-) or follows B

(B-A-), but no reduction in the response for the sequence C-A-. To examine this, we first selected those neurons (n = 74) for which (1) the first repetition adaptation index for A-A- was at least 0.33, i.e., those neurons showing a considerable degree of adaptation when stimulus A was repeated, and (2) the response to A and B differed by less than 33%, i.e., those neurons giving a similar response to A and B. Because the greatest reduction in response occurred between the first and second stimulus presentation, we focused the analysis on these two presentations. The response to A was not reduced when this stimulus followed the first presentation of C (Figure 3A: single neuron example; Figure 3B: population response [N = 74]). The response to A following C was significantly larger than when A was repeated (single neuron of Figure 3A: Mann-Whitney U test; p < 0.004; population response: post hoc Bonferroni t test; p < 0.000001; n = 74). Both the single cell (Mann-Whitney U test; p < 0.006) and the population response (post hoc Bonferroni t test; p < 0.000001; n = 74) were also significantly larger for A following B than when A was repeated. Note that stimuli A and B elicit similar responses on their first presentations in the single-cell example (Mann-Whitney U test on responses in the first presentation of the A-A and B-A- sequence; n.s.) and the selected sample of 74 neurons (paired t test; n.s.; n = 74). The response to A following B was only slightly smaller than to A following C (single neuron of Figure 3A: Mann-Whitney U test, n.s.; population response: post hoc Bonferroni t test; p < 0.00001; n = 74), despite the large difference in the responses to B and C on their first presentations in a sequence. The average degree of adaptation was very similar in the B-B- and A-A sequences, thus excluding the possibility that the weaker adaptation in the B-A- sequence was due to an inability of stimulus B to adapt the neuron.

A second, complementary selection consisted of those neurons in which the response to A following B (B-A- sequence) was decreased by at least 33% compared to the first presentation of A in the A-A- sequence and for which responses to A and B differed by less than 33% on their first presentations. However, only a small minority of neurons (20/169) fulfilled both these criteria. In these 20 neurons showing strong adaptation in the B-A- sequence, the average response to C following A was significantly larger than when A followed B (Bonferroni t test; p < 0.001; n = 20; Figure 3C). Even in these 20 neurons, the average response to B following A was larger than to the repetition of A, although this difference was small and not significant. Note that in 17 of these 20 neurons, the degree of adaptation when repeating A exceeded 33%, and thus these neurons are included in the sample of 74 neurons of Figure 3B. Selecting the 77 neurons that showed an adaptation larger than 33% in the A-A- or B-A- sequence and less than 33% response difference for A and B in their first presentation yielded results very similar to those obtained with the 74 neurons selected using the A-A- adaptation only. Thus, for the large majority of the neurons that respond similarly to A and B, the degree of adaptation is smaller for the successive presentation of two different stimuli than for a repetition of a stimulus, even when the two different stimuli (i.e., B and A) elicit, on average, a nearly identical response to their first presentation in a sequence. That
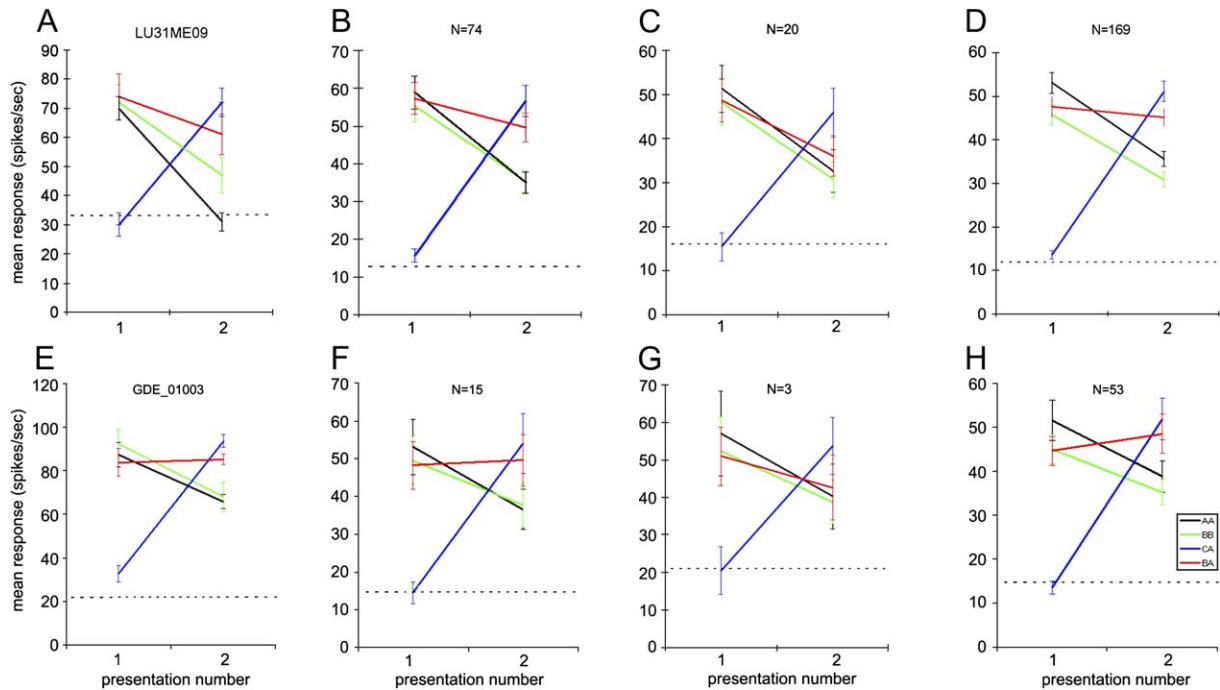
Figure 3. Responses to the First and Second Stimulus Presentations

(A–D) Adaptation test 1. (E–H) Adaptation test 2. (A and E) Example neuron. (B and F) Selected sample of neurons that adapted strongly in the A-A- sequence and responded similarly to the first presentation of images A and B. (C and G) Selected sample of neurons that adapted strongly in the B-A- sequence and responded similarly to the first presentation of images A and B. (D and H) Whole population tested. AA, repetition of A; BB, repetition of B; BA, A following B; CA, A following C. Error bars indicate standard errors of the mean. The mean baseline activity is shown by the stippled line. The same image (A) was shown in the second presentation of the AA, BA, and CA pairs (black square in Figure 1).

the overall weaker adaptation in the B-A- sequence is not a result from the selection criteria was confirmed by the similarity of the results obtained when averaging across all 169 neurons tested (Figure 3D), i.e., including those neurons that showed less adaptation than 33% and for which the difference in response between A and B was greater than 33%.

Examination of the average time course of the two selected sets of neurons (Figure 4) showed that the adaptation resulting from repeating the same stimulus (A-A-; B-B-) peaked at 150–200 ms after stimulus onset (also see Figure S2A). For the 74 neurons with strong adaptation to A and similar responses to the first presentations of A and B, the difference between the response to A following B and following another A is present from the response peak onward (Figure 4C; Figure S2B). In the very early phase of the response, responses to the second presentations of A in the A-A-, B-A-, and C-A- sequences are similar, except for slightly larger responses to A in the C-A- compared to the B-A- and A-A- sequences in the interval 50–70 ms after stimulus onset. Note that the latter reflect weak, initial responses of neurons with shorter than average response latencies. Because fMRI activations are presumed to reflect the entire response and not just the very initial response phase, the contribution of the latter to the fMRI responses is likely to be negligible. For the subset of 20 neurons with strong adaptation in the B-A- sequence (Figures 4B and 4D), the responses to A following C are larger than to A following B and to the repetition of A during the entire course of the response.

A model linking neural tuning and fMR-A (Piazza et al., 2004) assumes that a neuron adapts in direct proportion to the strength of its response to a stimulus. This predicts that the difference in percent between responses (%RD) to stimuli X and A on their first presentation (i.e., the stimulus selectivity) equals the difference in percent (%AD) between the percent adaptation in the X-A- sequence and percent adaptation in the A-A- sequence (see Experimental Procedures). Thus, if a neuron responds equally well to A and B (%RD = 0), the amount of adaptation in A-A- and B-A- conditions should be equal (%AD = 0), while a 50% difference in responses should produce a 50% difference in adaptation.

The prediction that %AD should equal %RD can be reliably tested for those neurons showing adaptation. Thus, we determined the relationship between %RD and %AD for those neurons having a first repetition adaptation index for the A-A sequence that was larger than 0.33. To exclude any possible biasing of the results that might arise from using this selection criterion, we also performed the correlation analysis of %RD and %AD for all neurons. Note that these analyses assume that the responses in the first presentation can be used to assess the stimulus selectivity of the responses of the neurons. This is a valid assumption because the mean responses to stimuli A (53 spikes/s), B (48 spikes/s), and C (13 spikes/s) obtained in the preliminary search test, a standard test to assess stimulus selectivity of neurons, compared very well with the mean responses to the first stimulus presentations of the sequences in adaptation test 1 (A, 52; B, 47; C, 12 spikes/s) for those neurons
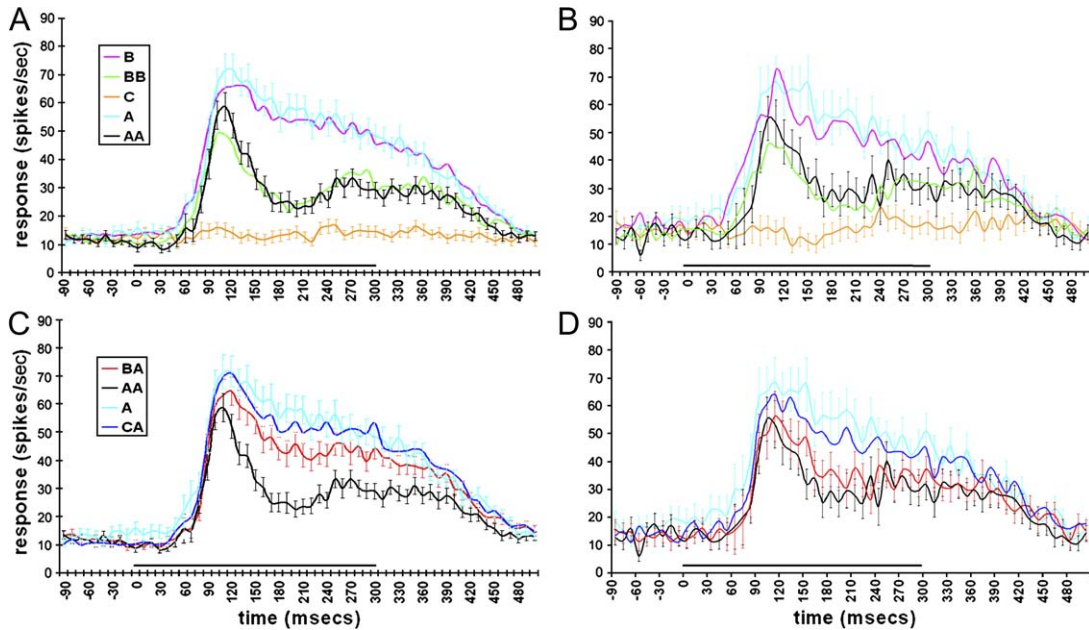
Figure 4. Population Peristimulus Time Histograms of Inferior Temporal Neurons that Adapted and Responded Similarly to Images A and B (Adaptation Test 1)

(A) Mean responses to the first presentation of stimulus A (light blue), B (red), and C (yellow) and to the repetition of A (AA; black) and B (BB; green) for the neurons with strong adaptation in the A-A- sequences (same 74 neurons as in Figure 3B). (C) Mean responses to A as first stimulus or following A (AA), B (BA; brown), or C (CA; dark blue). Same sample of neurons and conventions as in (A). (B–D). Mean responses for the neurons with strong adaptation in the B-A- sequences (same 20 neurons as in Figure 3C). Same conventions as in (A) and (C). Responses were averaged across neurons (unnormalized). Error bars indicate standard errors of the mean. The latter are shown for only four types of images to increase visibility. Stimulus presentation started at 0 ms and lasted until 300 ms. Binwidth = 10 ms.

(n = 159) for which sufficient search test trials were available.

Figure 5A shows that the postulated equality between %RD and %AD does not hold for the population of neurons with a first repetition adaptation index > 0.33 (n = 109 neurons), because most %AD values exceed 0%. To quantify the relationship between %RD and %AD, we performed two linear regression analyses, one using all 218 data points (a single neuron can contribute two data points, one for B-A and one for C-A) and one excluding data points with %RD > 100. Both regression analyses produced highly similar results (Figure 5A; Table 1). In both cases, the linear regression analysis revealed only a weak but significant positive correlation between %AD and %RD, with slopes significantly smaller than 1. More importantly, both intercepts were close to 60%, which is significantly larger than the predicted 0% (p < 0.0001). This indicates that when B and A produce an equal response (%RD = 0%), the degree of adaptation for A following B is still about 60% of the adaptation obtained when A is repeated.

Control analyses using all neurons (Table 1; Figure S3) confirmed the analyses that used only neurons with a first repetition adaptation index > 0.33 (Figure 5A). In addition to the regressions with and without data points having %RD > 100, we also performed regressions excluding outliers with %RD smaller than −100%. In each of the four analyses (Table 1), the intercept was above 50% and significantly different from 0. Note that this population of neurons was not selected using adaptation-related variables and thus is completely unbiased. Thus, we conclude that neuronal adaptation in IT shows a greater stimulus dependency than the responses.

The difference in stimulus selectivity between adaptation and responses is largely independent of the strength of the neurons' response to stimulus A. This was demonstrated by computing, for each neuron, the intercept (in %AD) of the line connecting the %RD-%AD values for the B-A- and C-A- sequences and plotting these intercepts as a function of the response of the neuron to the first presentation of A. Again, several analyses were conducted, each using different neuronal selection criteria: (1) all neurons, (2) only neurons with %RD < 100%, (3) neurons with a first repetition adaptation index > 0.33, and (4) a first repetition adaptation index > 0.33 and with %RD < 100%. In each of these four analyses, the Pearson correlation coefficients between response strength and %AD intercept were small, ranging from −0.12 to 0.02, and not significant (e.g., neurons with a first repetition adaptation index > 0.33, r = −0.12; n.s.; n = 109). Of the neurons selected with the same criteria as those of Figure 5 (stippled line), i.e., a first repetition adaptation index > 0.33 and %RD < 100%, the large majority have a %AD intercept value larger than 0%, even those neurons with responses above 100 spikes/s for the first presentation of A (Figure S1B). For this selected sample of neurons, the correlation coefficient between %AD intercept and response strength was −0.02 (n.s.; n = 56). The absence of a correlation between response strength and %AD intercept suggests that the greater selectivity for adaptation than for response is also present for stimuli that drive the neuron well.
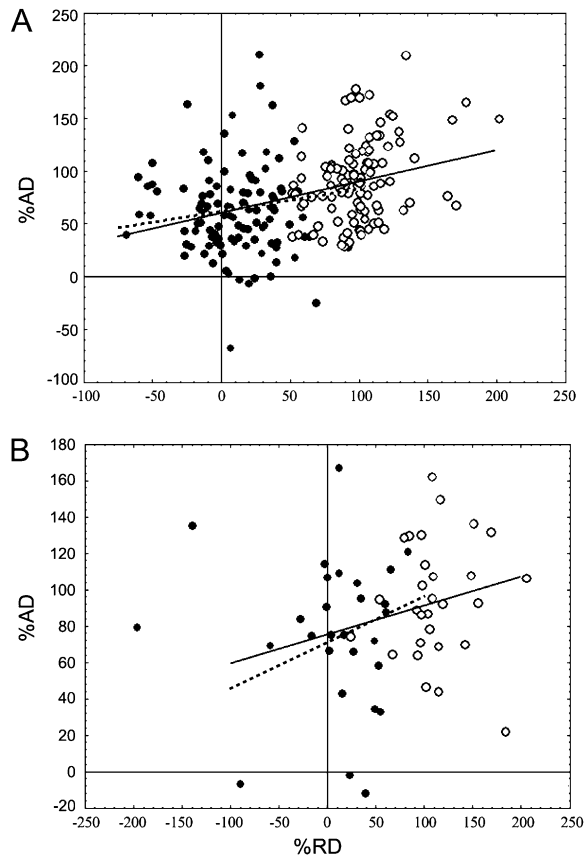
Figure 5. Correlation of Percent Response Difference and Percent Adaptation Difference

(A) Adaptation test 1. Population of neurons (n = 109) showing at least 33% adaptation for the repetition of A. (B) Adaptation test 2. Population of neurons (n = 29) showing at least 33% adaptation. Closed and open circles indicate data points for the BA and CA sequences, respectively. The lines indicate linear regression fits: solid line, all data points except outliers with %RD < −100%; stippled line, data points with %RD < 100 and > −100%.

The data presented so far were obtained using presentation durations and interstimulus intervals of 300 ms. Although these timing parameters are similar to those used in previous fMR-A studies, we also tested neurons with presentation durations and interstimulus intervals that ranged from 300 to 900 ms (Table 2). The responses for the 600 and 900 ms durations were analyzed using two windows, both starting 60 ms after stimulus onset. One window ended at stimulus offset, while the other one ended at 300 ms after stimulus onset, a value that corresponds to the stimulus offset for the tests with a 300 ms duration. The responses in tests of 300 ms duration were analyzed using the same analysis window of 240 ms. Including later phases of the responses for the 600 and 900 ms durations decreased the adaptation indices (Table 2; 540 and 840 bins). This was mainly due to a reduction of the response during stimulus presentation, producing similar response levels for the first and second presentations of a stimulus from about 400 ms after stimulus onset (data not shown). Given the small number of neurons tested with these stimulus timings, we performed the regressions for the %RD and %AD values using all neurons tested. Table 2 shows the median first repetition adaptation indices of all neurons tested and intercepts of the regression lines when data points with %RD > 100 are excluded (regressions performed on all data points and when excluding the occasional outlier with %RD < −100 produced similar results). Intercepts ranged from 37% to 65% AD and differed significantly from 0 in all but two instances (most likely because of the relatively small number of observations). This suggests that the difference between selectivity of neuronal adaptation and response holds for a wide range of timing parameters.

The larger adaptation for the first repetition of A compared to the other sequences might be due to an attentional effect because B and C are more "novel" that the repeated A. This can be addressed by examining the responses at later repetitions, because stimuli will become less novel with repetition. The differences in the mean response to A (even presentation numbers in Figure 6) between the A-A-, B-A-, and C-A- sequences are smaller at later repetitions compared to the first. The decreasing differences among the responses to A in the three sequences are very likely the result of the adaptation to A bridging the presentation of intervening stimuli B and C, a phenomenon which has been reported previously for more ventral temporal cortical regions (Brown et al., 1987; Miller et al., 1991b). However, the responses to A in the C-A- and B-A- sequences remain larger than those in the A-A- sequences (Figure 6; Figure S2). We performed the same eight regression analyses on %AD and %RD as above, but now using the responses at the third and tenth presentation to compute %AD, instead of the first and second presentations. Indeed, at the tenth presentation, the A stimuli in the A-A, B-A-,

Table 1. Results of Regression Analysis of %RD and %AD in Adaptation Test 1

	First versus Second				Third versus Tenth/RD1				Third versus Tenth/RD3			
	I	S	r	N	I	S	r	N	I	S	r	N
>33% adap	61*	0.30	0.37*	218	48*	0.19	0.13	85	53*	0.08	0.08	85
>33% adap; RD > −100	61*	0.30	0.37*	218	37*	0.34	0.21	83	54*	0.07	0.07	82
>33% adap; RD < 100	62*	0.21	0.22*	163	49*	0.17	0.09	65	51*	0.24	0.15	57
>33% adap; −100 < RD < 100	62*	0.21	0.22*	163	36*	0.45	0.19	63	49*	0.30	0.15	54
All	53*	0.29	0.21*	326	44*	0.29	0.11	248	44*	0.26	0.15*	248
All; RD > −100	56*	0.27	0.18*	323	39*	0.37	0.13*	246	47*	0.22	0.12	242
All; RD < 100	55*	0.22	0.14*	249	47*	0.14	0.04	195	44*	0.33	0.15*	169
All; −100 < RD < 100	59*	0.14	0.08	246	43*	0.24	0.07	193	48*	0.23	0.08	163

I, intercept %AD; S, slope; r, correlation coefficient; N, number of observations; >33% adap, neurons with >33% adaptation in A-A- sequence; All, all neurons; RD1 and RD3, response difference A versus B based on first and third presentation, respectively. *p < 0.05.

Table 2. Median First Repetition Adaptation Indices and %AD Intercepts for Adaptation Test 1 with Different Stimulus Durations and Interstimulus Intervals

Stimulus Duration	Interstimulus Interval	Analysis Window	Median Adaptation	N Neurons	Intercept %AD	N Data Points for Regression
300 ms	600 ms	240 ms	0.27	22	55*	34
300 ms	900 ms	240 ms	0.20	21	40	35
600 ms	300 ms	240 ms	0.36	23	43*	35
900 ms	300 ms	240 ms	0.36	20	60*	33
600 ms	300 ms	540 ms	0.22	23	65*	38
900 ms	300 ms	840 ms	0.21	20	37	35

*Significantly ($p < 0.05$) different from 0.

and C-A- sequences will be similar regarding novelty, as A will have been presented four times in the B-A- and C-A- conditions. The degree of adaptation was computed using the responses to A at the third presentation, also a less novel stimulus, as the reference and using net responses of at least five spikes/s. The adaptation between the third and tenth presentation of A amounted to 25% reduction in response and was significant (paired t test, $p < 0.00001$). %RD was computed using
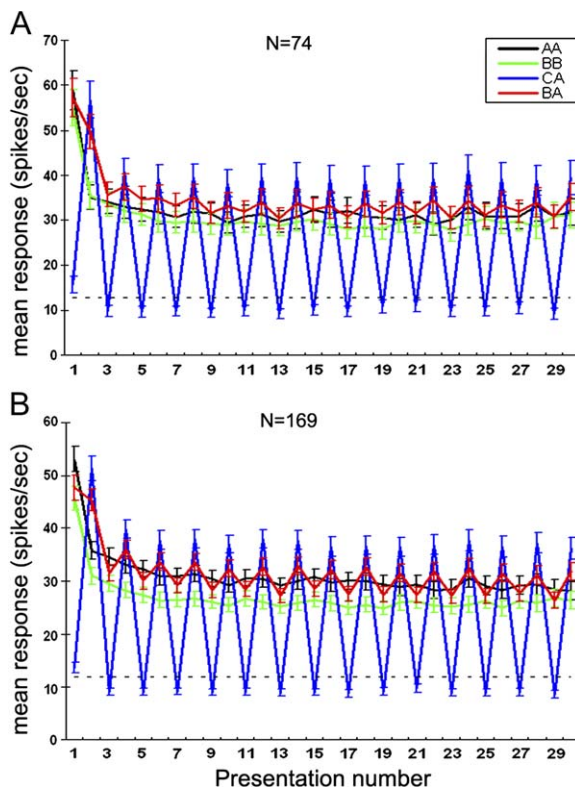

Figure 6. Population Response in the Different Stimulus Sequences Plotted as a Function of Presentation Number in Adaptation Test 1

(A) Selected population of 74 neurons that adapted by more than 33% and responded similarly to images A and B. (B) Whole population of 169 neurons. AA (black), repetition of A; BB (green), repetition of B; BA (red), alternation of B and A; CA (blue), alternation of C and A. Error bars indicate standard errors of the mean. The mean baseline activity is shown by the stippled line. Note that in the latter two sequences, the image on an odd number of presentations was either C or B, while on an even number of presentations A was presented. Thus, on an even number of presentations the same image (A) was present in the AA, BA, and CA sequences.

the response to either the first presentation or the third presentation in the A-A-, B-A-, and C-A- sequences. In each of the eight regression analyses (Table 1; Figure S3), the intercepts of the regression lines were significantly larger than 0, indicating less adaptation when switching between different stimuli than when repeating the same stimulus, even when these stimuli drive the neuron equally well and are similar with respect to novelty. However, the intercepts are smaller than for the first repetition analyses, indicating that at later repetitions the mismatch between selectivity of the response and adaptation is reduced, although still present.

Adaptation Test 2

In the first adaptation paradigm, one repeatedly adapts the neuron in the different sequence trials, though it is unclear what effect this repeated adaptation might have on the stimulus dependency of the adaptation effect. Also, it is uncertain whether similar effects might be obtained were the first presentation of A, B, or C not to occur at the beginning of a trial sequence, but rather in the midst of a sequence of other stimuli. To address this, we employed a second adaptation paradigm (Figure 1B), in which the pairs of "probe" stimuli, either A-A, B-B, B-A, or C-A, were imbedded in a 12 image sequence of other randomly chosen stimuli. At least three other images preceded the probe stimuli so that the adapting probe stimulus was not the first stimulus of a trial. Also, any stimulus was repeated no more than once in a sequence, in contrast to the multiple repetitions of the first paradigm. Stimulus duration and interstimulus interval were 300 ms.

We tested 53 responsive single IT neurons in the second adaptation paradigm. The median adaptation index for the A-A sequence was 0.34 (first quartile, 0.19; third quartile, 0.47; N = 53), which is somewhat smaller than that obtained with the first paradigm. Fifteen neurons fulfilled the criteria of an A-A adaptation index larger than 33% and a response difference between A and B smaller than 33%. For these 15 neurons, the initial responses to B and A did not differ significantly (paired t test; n.s.; n = 15). Analysis showed that the mean response decrease for stimulus A did not differ significantly between the B-A and C-A sequences (Figure 3E: individual neuron; Mann-Whitney U test: n.s.; Figure 3F: population response; post hoc Bonferroni t test; n.s. [n = 15]), and the responses to A in both sequences were significantly larger than that to A when it was repeated (Figure 3E; individual neuron; B-A versus A-A: Mann-Whitney U test; $p < 0.0002$; C-A versus A-A: Mann-Whitney U test; $p < 0.0001$; Figure 3F: population response [n = 15]: B-A

Table 3. Results of Regression Analysis of %RD and %AD
in Adaptation Test 2

	I	S	r	N
>33% adap	81*	0.08	0.16	58
>33% adap; RD > −100	73*	0.18	0.28*	56
>33% adap; RD < 100	80*	0.05	0.10	40
>33% adap; −100 < RD < 100	71*	0.25	0.30*	38
All	83*	0.15	0.18	103
All; RD > −100	79*	0.22	0.23*	101
All; RD < 100	82*	0.13	0.13	75
All; −100 < RD < 100	76*	0.27	0.21	73

I, intercept %AD; S, slope; r, correlation coefficient; N, number of observations; >33% adap, neurons with >33% adaptation in A-A- sequence; All, all neurons; *p < 0.05.

versus A-A: post hoc Bonferroni t test; p < 0.00007; C-A versus A-A; post hoc Bonferroni t test; p < 0.000001). Only three neurons showed a response reduction exceeding 33% in the B-A- sequence (Figure 3G); two of these had an adaptation effect larger than 33% when A was repeated and thus were included in the sample of 15 neurons shown in Figure 3F. For those 16 neurons with adaptations larger than 33% in the A-A- *or* in the B-A- sequence, the results were highly similar to those shown in the Figure 3F. Also, the population response of all 53 responsive neurons (Figure 3H) shows a significantly larger response in the B-A- compared to the A-A- sequence. Thus, as in the first adaptation paradigm, the adaptation effect is greater when the same stimulus is repeated than when two different stimuli are presented in succession, despite the similarity of the responses to these two stimuli on their initial presentation.

The same conclusion was supported when the regression analyses are performed on %RD and %AD (Figure 5B; Table 3) using the same selections as for adaptation test 1. Intercepts of the eight regression lines using different selections (Table 3) ranged between 71% and 82% AD, all significantly different from 0. Also, there was no significant correlation between response strength to the first presentation of A and the %AD intercept, computed using the same procedure as for adaptation test 1: correlation coefficients for the four different selections of neurons ranged from −0.14 to 0.03 (all n.s.). Thus, despite differences in stimulus presentation schedules, the results for the single repetition adaptation effects were similar in the two adaptation paradigms.

Discussion

The present results show that for single IT neurons the stimulus dependency of single-repetition adaptation differs from the stimulus selectivity of the neuron's responses. In two adaptation paradigms, we observed lower average response decreases when two stimuli that drive the neuron similarly were presented in succession than when one of the stimuli was repeated. This indicates that adaptation shows a greater stimulus selectivity than the responses themselves, a result obtained for a wide range of timing parameters.

One could argue that the larger neural response for the B-A- sequence than the repetition sequence is caused by more attention for novel compared to repeated stimuli. It should be noted that all stimuli in the

present study were quite familiar to the animals because they had been presented in many trials while searching for responsive neurons. Also, the monkeys' fixation was very similar and relatively stable for repeated and cross-stimulus presentations (see Experimental Procedures), as expected if all stimuli are equally familiar and of no interest to the monkey. If the stimulus-dependent nature of adaptation following a single presentation is a consequence of stimulus novelty, then this dependency should disappear after a few presentations, because the stimuli would no longer be novel. Under this assumption, that number of presentations has to be small, as the assumption implies that the high degree of stimulus dependency indicates a sharp decrease in novelty between first and second presentation. However, the stimulus dependency remained significant, although somewhat reduced, in the adaptation between the third and the tenth presentations. These stimuli can no longer be considered novel, suggesting that the stimulus dependency does not simply reflect "novelty." Furthermore, note that the decrease in the stimulus dependency of adaptation with repetition might not reflect changes in attention, but ill understood effects of intervening stimuli upon adaptation. Similarly, the delayed time course of the adaptation effect relative to response onset does not necessarily indicate attention-related feedback from other areas, but may reflect processing in intra-areal circuits. Finally, indirect evidence that the stimulus dependency of adaptation is not caused by attentional differences comes from fMR-A, which is presumed to reflect neural adaptation: fMR-A differences for sequences of "identical" versus "different" shapes were similar in human LOC whether stimuli were presented during passive fixation or in a condition in which the stimuli had to be attended (Kourtzi and Kanwisher, 2001), and in both human LOC and monkey IT under passive fixation and attention-equated conditions (Sawamura et al., 2005). Thus, we believe that differences in attention cannot explain the stimulus-dependent adaptation. Instead, the decrease in neural response might underlie an automatic mechanism to reduce the saliency of repeated stimuli (see Fahy et al., 1993; Miller et al., 1993; Xiang and Brown, 1998).

The stimulus dependency of the adaptation in IT neurons shows that it is unlikely to result from action potential-dependent postsynaptic mechanisms (e.g., tonic hyperpolarization [Carandini and Ferster, 1997; Sanchez-Vives et al., 2000] or "fatigue"). Were that the case, adaptation would transfer across stimuli and be purely response dependent. The stimulus dependency of the response suppression suggests that it occurs locally at the level of the synapses onto the neuron (e.g., local synaptic depression) and/or in neurons in the same or other regions that provide input to the adapting neuron. In the former case, the degree of cross-adaptation for two different stimuli will be a function of the number of synapses common to the processing of the two stimuli by the adapting neuron. In the latter case, cross-adaptation will correlate with the number of neurons that can be adapted, that respond to features common to the two stimuli, and that provide input to the neuron being tested. These adapting neurons can be located either in different areas that provide input to IT or in IT itself. In each of these cases, adaptation of single IT

neurons reflects selectivity at the input rather than at the output level of a neuron and thus does not need to correlate with the action potential-based stimulus selectivity of single neurons.

Previous studies in ventral IT and perirhinal cortex have suggested the presence of stimulus-specific adaptation (Fahy et al., 1993; Li et al., 1993, Ringo, 1996; Xiang and Brown, 1998) but did not relate it to preadaptive response strength or stimulus selectivity as we did here for dorso-lateral TE neurons. One can distinguish two sorts of (interrelated) adaptation effects (Li et al., 1993; Fahy et al., 1993; Vogels et al., 1995; Ringo, 1996; Xiang and Brown, 1998): a response decrease for familiar compared to novel stimuli, the so called "familiarity effect," and a decrease in responses induced by repetition of already familiar stimuli. The latter, which was investigated in the present study, seems to be reset at the start of a new trial (Miller et al., 1993), even during a passive fixation task (Vogels et al., 1995; present results), while the familiarity effect has been reported to bridge intervals of at least 24 hr, with many intervening stimuli (Fahy et al., 1993; Xiang and Brown, 1998). Indirect evidence suggests that familiarity-related adaptation is also stimulus dependent (Miller et al., 1991b, Li et al.1993; Xiang and Brown, 1998; Ringo, 1996).

Studies in macaque early visual areas suggest that different forms of neuronal adaptation in visual cortex are stimulus dependent. One series of experiments (Lisberger and Movshon, 1999; Priebe and Lisberger, 2002; Priebe et al., 2002) studied short-term adaptation (recovery time constant of 86 ms; Priebe and Lisberger, 2002) that produces transient responses to motion stimuli in extrastriate area MT/V5 and concluded that this adaptation mechanism does not depend on an intrinsic, action potential-based mechanism but depends on the input from other MT/V5 neurons (Priebe et al., 2002). Other studies using long-duration adapting stimuli (30 s or more) showed stimulus-specific adaptation effects in areas V1 (Carandini et al., 1997) and MT/V5 (Kohn and Movshon, 2003) of anesthetized animals. Recently, Tolias et al. (2005) reported that changing the direction of motion of a random dot pattern immediately after a 1 s adaptation period affects the responses of V4 neurons, even those that are not direction selective, in line with the suggestion that adaptation occurs at the level of inputs to the neurons. Stimulus-specific adaptation has also been found in the auditory cortex of anesthetized cats (Ulanovsky et al., 2003), suggesting that it is not a property that is unique to the visual modality.

The present data are most relevant for fMR-A paradigms in which two stimuli are presented in succession separated by a brief interval ("short lag, immediate repetition"; e.g., Kourtzi and Kanwisher, 2000, 2001; Kourtzi et al., 2003a, 2003b; Piazza et al., 2004; Winston et al., 2004; Epstein et al., 2003; Boynton and Finney, 2003). The neural adaptation we observed with single repetition might underlie the fMRI adaptation seen in single-repetition event-related paradigms, except that the degree of adaptation seems not to match well. In order to predict the degree of fMR-A given the observed neural adaptation, we convolved the neural responses with hemodynamic response functions (HRF; Boynton et al., 1996; Figure S4). We performed the convolution for an "identical" condition consisting of the average net neural re-

sponses in the first two presentations of the A-A- sequence (adaptation) and for a "different" condition consisting of a succession of the average net neural responses to the first presentation of A with an interstimulus interval of 300 ms (no adaptation). Because the HRF is sluggish and of much longer time course (>10 s) than the relatively brief succession of neural responses (<1 s), the relative difference between the predicted BOLD responses for the "identical" and "different" conditions is smaller than the average neural adaptation but similar to that observed in fMR-A studies (Figure S4). Indeed, the percent difference of the predicted peak BOLD response between the "different" and "identical" conditions, relative to the peak BOLD in the "different" conditions, ranged between 21% and 22%, depending on the parameters of the HRF. Values of the same order were observed in human event-related single-repetition fMR-A studies comparing BOLD responses in LOC between "identical" and "different" object conditions. Computing approximate percent BOLD differences from the figures yielded values of 30% (Epstein et al., 2003), 15% (Kourtzi and Kanwisher, 2000), and 25% (Kourtzi and Kanwisher, 2001).

Other fMR-A studies have employed "long-lag repetition" paradigms (Henson, 2003) that are more closely related to classic behavioral priming paradigms: a set of (familiar or novel) stimuli are shown and then followed, after an interval that can range from minutes to days, by a second set including the previously shown stimuli (e.g., Buckner et al., 1998; James et al., 2002, Vuilleumier et al., 2002; George et al., 1999; Chao et al., 2002; Van Turennout et al., 2000). Interpreting long-lag adaptation paradigms is complicated by the fact that the precise relationship between the long-lag repetition fMRI effects and the reduction in single-cell responses induced by stimulus repetition is still unclear (see Henson and Rugg, 2003; Henson, 2003).

What are the implications of the present single-cell data for the interpretation of fMR-A data? First, adaptation was present in the B-A- sequences, implying that, on average, two stimuli that drive the same neuron will elicit some cross-adaptation. Adaptation was in general very weak if not absent in the C-A- condition, implying that a stimulus that does not excite the neuron will produce little adaptation. Thus, when fMRI adaptation is present for a pair of stimuli, one might conclude that these stimuli excite the same neurons, suggesting that fMR-A might be an effective tool for demonstrating the invariant properties of neurons. Second, for single repetitions, the average degree of cross-adaptation for the B-A- sequences was only about half of what would be expected from the tuning of the neuron, implying that tunings estimated from adaptation may overestimate the actual tuning of a neuron. This problem might be smaller for "block" design compared to "single-repetition, event-related" designs because the mismatch of the response selectivity and adaptation decreased with repetition.

Unquestionably, data on the stimulus selectivity in different human brain regions are much needed, and fMR-A paradigms have attempted to provide these data. However, the present study shows that the link between fMR-A and neuronal tuning is far from straightforward. Ascertaining the correct interpretation of fMR-A

data will require further single-cell studies and most particularly the combination of fMR-A and single-cell work in the monkey.

Experimental Procedures

Subjects and Recording

Two (M7 and G) male rhesus monkeys (*Macaca mulatta*) served as subjects. Animal care and experimental procedures met the national and European guidelines and were approved by the Ethical Committee of the K.U. Leuven Medical School. Both monkeys had a plastic headpost and recording chamber fixed to the skull with acrylic cement and ceramic screws. The surgical implants were performed under aseptic conditions and deep gas anesthesia (mixture of 1.5 MAC isoflurane and 50%N_2O/50% O_2). The positioning of the recording chamber was guided by a preoperative MRI and the anterior-posterior and medio-lateral recording positions were verified by MRI scans obtained in the midst of the recording sessions. For the latter, a glass tube filled with a copper sulfate solution was inserted into the recording chamber grid (Crist Instruments) at one of the guiding tube positions. Visualization of these markers as well as of blood residues from guiding tube injuries allowed a reliable estimation of recording positions. The depths of the recording positions were estimated using microdrive depth readings corresponding to gray/white matter transitions and to contacts with the skull basis that were obtained during the recordings.

The recording locations were based on the activations obtained in our previous monkey fMRI adaptation study (Sawamura et al., 2005), which included one of the animals (M7) used in the present study. The activation was defined by subtraction of the fMRI signal in blocks in which the same object image was repeated 32 times from blocks in which 32 different images of objects were presented (subtraction "32 objects" – "identical" of Sawamura et al., 2005). Across animals, the recording locations were estimated to range from 14 to 20 mm anterior to the external auditory meatus and included the ventral bank of the superior temporal sulcus and the lateral convexity. The recording positions were estimated to be lateral to the anterior middle temporal sulcus. Figure S5 shows a coronal MRI image of each animal at a representative recording position, in addition to the fMRI activation in M7. Note the correspondence of the fMRI activation and the recording site.

Extracellular recordings were made using standard, previously published techniques (Op de Beeck et al., 2001). In short, a tungsten microelectrode (1–2 Mohm measured in situ; Frederic Haer) was lowered through a guiding tube position in a Crist grid, connected with a Narishige microdrive that was firmly positioned on the recording chamber. Signals were filtered and amplified, and single spikes were isolated online using a Plexon system. Discriminated spike times were saved (1000 Hz resolution), together with trial and behavioral events, using a PC.

Fixation Task

Eye position was measured online with the ISCAN pupil tracking system (120 Hz). The animals were trained to foveate a small square (size = 0.1°). After a fixation of 580 ms, the stimuli were presented in one of the sequences shown in Figure 1. A trial comprising such a sequence was continued as long as the animal kept his gaze within a 2°–2.5° diameter window and until all 30 (adaptation test 1) or 12 stimuli (adaptation test 2) were presented. Juice reward was delivered to the monkey while he was maintaining fixation, using a reinforcement schedule in which the interval between two successive rewards decreased and the amount of reward increased as a function of fixation duration.

Eye positions were not saved during the recordings. After the recordings, we measured the eye position for 16 presentations of adaptation test 1 in each monkey. Stimuli used in the actual recordings (n = 15 tests) as well as novel A, B, and C stimuli chosen from our stimulus set (n = 17 tests) were presented in sequences as during the recordings and employing the same size of the fixation window. The within-trial standard deviation of the eye position, measured in a 600 ms interval starting at the onset of the second stimulus presentation and averaged across trials, equaled 0.06° and 0.07° for the x direction in monkeys M7 and G, respectively, and 0.12° and 0.15°

in the y direction. This standard deviation did not differ significantly in either direction among the A-A-, B-A-, and C-A- sequences (ANOVA; n.s., n = 32; across animals, the mean within-trial standard deviations for the three different conditions differing by less than 0.003° and 0.007° in the x and y direction, respectively). The same was true when restricting the analysis of eye positions to the 300 ms presentation of the second stimulus. This suggests that also during the recording sessions the monkeys fixated equally well during the second stimulus presentations in these three sequences.

For the initial test of selectivity, stimuli were presented for 300 ms during fixation, one per trial, followed by a reward.

Stimuli

The stimuli were grayscale (n = 128) and color (n = 128) drawings of objects (including animals) taken from Rossion and Pourtois (2004) (downloaded from http://www.cog.brown.edu/~tarr/stimuli.html; courtesy of M.J. Tarr, Brown University, RI). They were presented on a uniform gray background (10 and 17 cd/m^2 for grayscale and color images, respectively) and measured about 7° × 7° visual angle. Because these stimuli differ with regard to a rich set of moderately complex features (Tanaka et al., 1991), they are well suited for obtaining strong selective IT responses. The grayscale images have been used before in the monkey-human fMRI study of Sawamura et al. (2005).

Data Analysis

For the standard tests and analyses with presentation durations and interstimulus intervals of 300 ms, spikes were counted in each trial by using analysis windows that started 60 ms and ended 360 ms after stimulus onset, respectively. As baseline, we took the number of spikes in the 300 ms interval immediately preceding the onset of the first stimulus presentation in a trial. Analysis windows for tests with other timing parameters are given in Results. Mean responses to each stimulus at a particular position in a sequence were computed by averaging the spike counts across trials.

The plots of the population responses as a function of the number of stimulus presentations (Figures 2 and 6) are based on averages of the mean response of those neurons for which data were available. The number of available data declined with the number of presentations, with a minimum of 133 neurons at presentation 30. Note that when comparing the first and second presentations all neurons are used.

The *n*th repetition adaptation index for stimulus X is defined as

$$(rX - rXn)/rX,$$

with rX being the (baseline subtracted) net response to the first presentation of X and rXn being the net response to the *n*th repetition of X. An adaptation index of 0 and 1 indicates no and complete adaptation, respectively.

The percent response difference, %RD, between stimuli A and X is defined as

$$[(rA - rX)/rA] \times 100.$$

This was computed using net responses to the first presentations of A, B, and C (rX being the response to either B or C) for each neuron. A %RD of 0% indicates an equal response to A and X, while 100% indicates zero net response to X.

The percent adaptation difference, %AD, for X was the percent difference between the first repetition adaptation index for A and the response decrease for A following X:

$$100 \times \{[(rA - rA1)/rA] - [(rA - rXA)/rA]\}/[(rA - rA1)/rA],$$

with rXA being the response to A following X, and rA1 the response to the first repetition of A (A following A). A %AD of 0% indicates equal response reductions for X following A and for the repetition of A, while a %AD of 100% indicates no response reduction for A following X. Similarly, %AD_AA-BB, the percent adaptation difference between the AA and BB sequences was

$$100 \times \{[(rA - rA1)/rA] - [(rB - rB1)/rB]\}/[(rA - rA1)/rA],$$

with rB being the response to B in the first presentation, and rB1 the response to the first repetition of B.

A simple model assumes that the amount of adaptation is proportional to response strength (Piazza et al., 2004). This can be formalized as

$$rXA = (1 - a) \times rA$$

with adaptation factor

$$a = [rX/rmax] \times c,$$

rX being the response to X on the first presentation, rmax the maximal response of the neuron, and c being a constant defining how much the neuron adapts when optimally stimulated. This constant c can differ between neurons, with some neurons showing stronger adaptation than others. Thus,

$$rA1 = (1 - [rA/rmax] \times c) \times rA,$$

and

$$rXA = (1 - [rX/rmax] \times c) \times rA.$$

When inserting the equations for rA1 and rXA in the formula defining AD, the latter can be reduced to

$$(rA - rX)/rA,$$

which corresponds to the RD for stimuli A and X. Thus, when the amount of adaptation is proportional to the tuning of the neuron, %RD equals %AD.

Regression analyses were carried out using eight different selections (Table 1) consisting of all combinations of the following criteria: (1) all neurons versus those with an adaptation index for A larger than 33%, (2) all neurons versus removal of outliers with %RD > −100%, and (3) all neurons versus %RD < 100%. The rationale for the latter selection is that %RD values less than 100% reflect inhibition by stimulus C, and it is unclear what effect inhibition might have on adaptation. For all regressions, outliers with %AD values larger or smaller than 400% or −400% were removed.

Supplemental Data

The Supplemental Data for this article can be found online at http://www.neuron.org/cgi/content/full/49/2/307/DC1/.

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