Within- and between- hemifield generalization of repetition suppression in inferior temporal cortex.

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Running head: Spatial generalization of adaptation in IT.

Abstract

The decrease in response with stimulus repetition is a common property observed in many sensory brain areas. This repetition suppression (RS) is ubiquitous in neurons of macaque inferior temporal (IT) cortex, the end-stage of the ventral visual pathway. The neural mechanisms of RS in IT are still unclear, and one possibility is that it is inherited from areas upstream to IT that show also RS. Since neurons in IT have larger receptive fields compared to earlier visual areas, we examined the inheritance hypothesis by presenting adapter and test stimuli at widely different spatial locations along both vertical and horizontal meridians, and across hemifields. RS was present for distances between adapter and test stimuli up to 22°, and when the two stimuli were presented in different hemifields. Also, we examined the position tolerance of the stimulus selectivity of adaptation by comparing the responses to a test stimulus following the same (repetition trial) or a different adapter (alternation trial) at a different position than the test stimulus. Stimulus-selective adaptation was still present and consistently stronger in the later phase of the response for distances up to 18°. Finally, we observed stimulus-selective adaptation in repetition trials even without a measurable excitatory response to the adapter stimulus. To accommodate these and previous data, we propose that at least part of the stimulus-selective adaptation in IT is based on short-term plasticity mechanisms within IT and/or reflects top-down activity from areas downstream to IT.

New and Noteworthy

Neurons in inferior temporal cortex reduce their response when stimuli are repeated.

To assess whether this repetition suppression is inherited from upstream visual areas, we examined the extent of its spatial generalization. We observed stimulus-selective adaptation when adapter and test stimuli were presented at widely different spatial positions and in different hemifields. These data suggest that at least part of the repetition suppression originates within inferior temporal cortex and/or reflects feedback from downstream areas.

Keywords: Nonhuman Primate, Ventral stream, Repetition Suppression, Inferotemporal Cortex, Receptive fields.

Introduction

Brain areas in several species show adaptation: the neural responses to a stimulus can change during and/or after exposure to a stimulus. Repeating a stimulus usually, but not always, results in a suppression of the response (repetition suppression (Desimone 1996)). RS is fundamental for understanding processing during natural vision since it relates to the effect of a stimulus on the following stimulus, which occurs during daily vision (Whitmire and Stanley 2016). Also, the widely used fMRI adaptation paradigm (Malach 2012) in studies of normal and patient populations (Ewbank et al. 2017; Ewbank et al. 2015; Perrachione et al. 2016) makes it important to understand the neural mechanisms of RS.

RS is a common observation in macaque inferior temporal (IT) cortex (Vogels 2016). Here, we will be dealing with short-term repetition effects, i.e. those occurring in paradigms in which two or more stimuli, adapter and test, are presented sequentially for a brief duration (300-500 ms), separated by a relatively short interstimulus interval (300-1000 ms). These short-term repetition effects should be distinguished from familiarity effects that occur when a novel stimulus becomes familiar with repetition during a longer period, even across days (Fahy et al. 1993; Vogels 2016).

The neural mechanisms underlying RS in IT are still unclear. Firing rate dependent “fatigue” mechanisms intrinsic to the adapted neuron, such as prolonged after-hyperpolarization due to activation of membrane ion channels (Abolafia et al. 2011; Sanchez-Vives et al. 2000a; b) play only a minor, if any, role (Fabbrini et al. 2019). This, in agreement with other studies (De Baene and Vogels 2010; Sawamura et al. 2006), suggests that RS in IT results from synaptic mechanisms (e.g. synaptic depression (Zucker and Regehr 2002), but see (Fabbrini et al. 2019)) and/or suppressed input to the neuron. The suppressed

input can result from other IT neurons that provide excitatory input to the recorded neuron or from enhanced inhibition by interneurons. Apart from these local mechanisms within IT, RS may be inherited from upstream areas because short-term adaptation is present in areas upstream to IT, even V1 (Hansen and Dragoi 2011; Westerberg et al. 2019). Such inheritance of adaptation effects has been shown in dorsal stream area MT (Patterson et al. 2014) and mice visual cortex (Dhruv and Carandini 2014). Because of the smaller receptive fields (RF) at earlier visual areas, one can address the inheritance of adaptation by examining the spatial generalization of RS, as has been done in the dorsal visual stream (Kohn and Movshon 2003; Larsson and Harrison 2015; Priebe et al. 2002).

If the adaptation originates in earlier areas with smaller RFs, it should be absent when adapter and test stimuli do not spatially overlap and stimulate different RFs of upstream areas. Previously, we observed reduced but not absent RS in IT when adapter and test stimulus position differed by 8° (De Baene and Vogels 2010) or 10° (Kuravi and Vogels 2017) for 5-7° stimuli that were presented at 4-5° eccentricity along the vertical meridian. We concluded that at least part of the IT RS was not inherited from neurons in early visual areas such as V1, V2 and likely V4, based on their RF sizes at these eccentricities. More anterior shape selective visual areas (e.g. areas OTd and PIT (Janssens et al. 2014; Kolster et al. 2014)), providing input to anterior IT, have larger RFs and thus may contribute to the spatial tolerance of RS we observed there. For instance, the ventral bank of the superior temporal sulcus (STS) in PIT, a region which projects to the anterior ventral bank of the STS where the recordings were made in the IT studies, contains neurons with RF sizes of 10° at small eccentricities (Hikosaka 1998). Thus, to measure the width of the spatial tolerance and in an attempt to exclude full inheritance of RS in anterior IT from these upstream ventral

visual areas, we employed a range of distances between adapter and test stimuli along both vertical and horizontal meridians.

A second novelty of our study is that we examined the generalization of RS across hemifields in macaque IT. Indeed, anterior IT neurons have a wider representation of the ipsilateral visual field (Desimone and Gross 1979; Op De Beeck and Vogels 2000) than posterior ventral visual areas (Boussaoud et al. 1991; Hikosaka 1998). Hence, we predicted that if at least part of the RS originates in IT, it should be present when the adapter and test stimuli are presented in different hemifields. To examine the spatial generalization of RS in anterior IT across hemifields, we presented adapter and test stimuli at widely different spatial positions across the two hemifields.

Adaptation in IT is known to depend on the identity of the adapter and test stimuli, i.e. stimulus selective, which has been hypothesized to result from selectively suppressed input to the IT neuron (Sawamura et al. 2006). Thus, in addition to examining the responses to repetitions of the same stimulus, we also measured responses to test stimuli that were preceded by different adapters, assessing stimulus-selective adaptation. Stimulus-selective adaptation was measured when adapter and test stimuli were presented at different positions within the same or different hemifields. When the stimulus selectivity of adaptation is inherited from upstream areas, it should not remain when adapter and test stimuli greatly differ in position, while it can generalize across positions when originating in IT.

Materials and Methods

Subjects

Two rhesus macaques (*Macaca mulatta*; both male) served as subjects. Animal care and experiments were carried out in accordance with the national and European guidelines and were approved by the Animal Ethics Committee of the KU Leuven. Details about implants and surgery can be found in (Kaliukhovich and Vogels 2011), and will only be briefly summarized here. We implanted an MRI compatible headpost and recording chamber. The placement of the recording chamber was guided with a preoperative MRI scan and verified with MRI scans between recording sessions. Reliable estimations of the recording positions were obtained by the visualization of glass capillaries that were inserted into the recording chamber grid (Crist Instrument), filled with a 1% solution of the gadolinium-based contrast agent Gadoteric acid (Dotarem), at predetermined positions. Since no histology is available, recording positions were estimated based on the MRI visualization of these markers combined with the microdrive depth readings of the white/gray matter transitions relative to the grid base.

Recordings were made from the lower bank of the superior temporal sulcus (STS) of the anterior IT cortex. The anterior-posterior coordinates of the estimated recording positions ranged between 16 and 22 mm, and 18 and 20 mm, anterior to the auditory meatus, in monkeys M1 and M2, respectively, whereas the corresponding medial-lateral coordinates in those monkeys ranged between 21 and 24 mm and 21 and 23 mm, lateral to the midline.

Recordings

Spiking activity was recorded simultaneously with an 8-channel S-Probe (Plexon). The intercontact (-channel) spacing was 100 μm with electrode sites linearly arranged on a single shaft. The S-Probe was lowered with a Narishige microdrive through a guide tube that was fixed in a Crist grid. The S-Probe was positioned so that visually driven multi-unit activity (MUA) was present on most if not all channels. After positioning the S-Probe in the STS, we waited for at least 1 h before performing the recordings to ensure good recording stability.

Recordings were made with an INTAN data acquisition system. Recorded signals were preamplified, bandpassed filtered between 500 and 7500 Hz and saved at 30 kHz. Spike sorting was performed offline using Plexon Offline Sorter, blind to any experimental conditions. Before spike sorting, the signal was re-referenced using the common median reference procedure (Rolston et al. 2009), which removes artefacts common to all channels. For each channel, at least one unit and occasionally two units were identified. Note that in the large majority of cases, these units were not well-isolated single neurons but multi-unit clusters. Throughout the paper, we refer to these multi-unit clusters as “units”. For each identified unit we computed the signal-to-noise ratio (SNR), using the same procedure of (Kelly et al. 2007), as an index of the sorting quality. We performed a separate analysis for units with an SNR > 3 (10% of units). Because the results were similar for the latter units and the units with lower SNR, we pooled all units in the analyses presented in this paper.

Four units were recorded with tungsten microelectrodes (125 μm diameter). In those cases, the signal was amplified (Bak amplifier) and bandpass filtered between 600 and 5000 Hz, and the raw voltage signal was saved at 40 kHz. The recordings and the offline sorting were performed using the same procedure as described above, with the exception of the

common median reference preprocessing, which cannot be performed on signals recorded from a single electrode.

Visual Stimuli

We employed two stimulus sets, both consisting of 50 color images. In the first set, identical to that used in previous studies (Fabbrini et al. 2019), the stimuli were composed of several animate and inanimate images including animals, faces and objects. The second set consisted of animals (purchased from the Shutterstock database (<https://www.shutterstock.com/>)) and fractals (generated using the fractal-based algorithm of (Miyashita et al. 1991)). In addition, we used a white square as a control stimulus. The vertical or horizontal extent of the images was 3° of visual angle. Stimuli were displayed on a CRT monitor (1024x768 pixels at 75 Hz; ViewSonic G225F) on a grey background at an eye-distance of about 58 cm. Eye position was continuously tracked by means of a video-based eye tracker using one eye (SR Research EyeLink; sampling rate 500 Hz).

Tests

Search test

After a 1-h waiting period, the two images to be used during the subsequent adaptation test were selected by means of a Search test. We presented the 50 images while the animal was performing a passive fixation task. On each trial, the monkeys were required to maintain their gaze within a 2° diameter fixation window surrounding a square-shaped red fixation target (size, 0.19°) that was presented in the center of the monitor and visible during the entire trial. A trial started with the onset of the fixation target. After 300 ms of stable fixation, a stimulus was presented for 200 ms. To complete a trial and obtain a fluid reward, the monkeys had to maintain fixation for 200 ms post-stimulus offset. The images

were presented at the center of the screen in a random order. On the basis of the spiking activity to the stimuli in the different channels, we selected two images that elicited a response in several of the channels.

Adaptation test

Using the two selected images, A and B, we employed the following adaptation test (Figure 1A). Monkeys were required to fixate the fixation target that was shown at the center of the monitor and visible during the entire trial. After a 500ms fixation period, a stimulus was presented for 300ms, which served as adapter (S1), and could be either the selected A or B stimulus. After the presentation of the adapter, there was an interstimulus interval of 400ms, followed by presentation of the test stimulus (S2), which lasted 300 ms. As for the adapter, the test stimulus was either A or B. To complete a trial and obtain a fluid reward, the monkeys had to maintain fixation for another 500 ms after offset of the test stimulus. Any break in fixation during the 2000 ms interval aborted the trial. After delivering the reward, we presented a full-field scrambled visual scene for 500 ms followed by a blank screen for 2000 ms. During the latter period, the monkeys were not required to fixate. The presentation of the scrambled stimulus served to reduce the carry-over of visual adaptation effects from the adapter and test stimuli to the subsequent trial.

The position of the adapter and the test stimuli were manipulated independently. S1 could be presented at 8 different positions (Figure 1B): at the center, at 8° and 16° eccentricity on the horizontal meridian in the contralateral visual field, at 6° and 12° eccentricity on the vertical meridian in the upper and lower visual field and at 6° eccentricity on the horizontal meridian in the ipsilateral visual field. For each of these S1 positions, S2 could be presented at two different positions: at the center, or at one of the four 6° or 8°

positions (see Figure 1C). Because of the limited recording duration, we could not present S2 at all S1 positions. During the initial phase of the experiment, we presented S2 at larger eccentricities (16° in the contralateral visual field instead of 8° in 15 and 10 electrode penetrations in M1 and M2, respectively, and 12° in the upper and lower visual field instead of 6° in 6 electrode penetrations in M1), but the data of these conditions were not included in the analyses. Later, we opted to present S2 at positions of maximally 8° eccentricity, which because of the typical receptive field size of IT neurons (Op De Beeck and Vogels 2000) increases the likelihood of having responses to S2.

Note that each S1 position predicted two S2 positions with an equal probability of 0.50, and thus all presented S1-S2 sequences had the same transitional probability. Because of this design, differences in S2 response, following different S1 positions, must be due to the preceding S1 position and do not result from statistical learning of transitional probabilities of position. As a further control for statistical learning effects, we presented a white square at 16° eccentricity in the ipsilateral visual field with S2 being presented at the center or at 16 ° eccentricity in the contralateral visual field. The S2 stimulus could be either the A or B stimulus, with an equal probability. We expected very weak IT responses to this “simple” stimulus presented at this far ipsilateral position, but it predicted the center S2 with the same transitional probability as in the other S1-center S2 sequences. The difference between the responses to the center S1 and center S2 following the square would provide the upper bound of a potential statistical learning effect of position determining response differences between S1 and S2.

The total number of conditions (defined as a different combination of S1 and S2 in a trial) was 68 (2 stimuli (A, B) x 2 trial types (repetition (AA, BB) versus alternation (AB, BA)) x

8 adapter positions x 2 test positions, plus 4 control conditions). The conditions were presented in random order, with a minimum of 6 trials/condition (median: 10 trials/condition).

Data analysis

Data analyses were performed using custom scripts written in Matlab (MathWorks). Unless otherwise stated, we quantified the response by computing the mean firing rate in a 300 ms long analysis window that started 50 ms after stimulus onset. Adapter and test stimuli onsets were detected by a photodiode (invisible to the monkey) and those timings were employed to align the neural activity to the stimuli for the two stimulus types separately. For each unit, we defined the effective stimulus as the one (of A and B) that elicited the highest response when presented as S1.

We determined the stability of each recorded unit in two complementary ways. First, similar to the procedure by (Roth and Rust 2019), which is based on the Fano factor, we computed the Fano factor by linear regression of the relationship between the mean and the variance of the trial-wise responses to S1 across all conditions. We considered units with a Fano factor > 4 as being unstable and these were not analyzed further. Second, we took the responses to the effective stimulus when presented as S1 at the position that elicited the maximum response. Trials of the recording period were divided in 4 successive, equally sized blocks, and the mean firing rate of each block was computed. The mean of each block had to fall inside the interval of ± 2 * standard error of the mean response to S1, computed across all trials in which the effective stimulus was presented at that position. Otherwise, the unit was deemed to be unstable and not analyzed further. The standard error of the mean responses

to S1 was computed assuming a Fano factor of 4. A unit was included when it fulfilled both criteria of recording stability.

To avoid biases in responses in particular conditions and hence artefactual statistics, selection criteria for including units differed between analyses. When examining the responses to S1 as a function of visual field position (Figure 2), we selected units by comparing the response to the effective stimulus presented as adapter with the baseline activity measured within the 100 ms window directly preceding S1 onset of the same trial (two-sided Wilcoxon signed rank test, $p < 0.05$). For this statistical test, the trials of the 4 conditions in which the stimulus was presented as S1 at the tested position were pooled. Units that showed a significant excitatory response for at least one of the S1 positions were selected.

We examined RS by comparing the response between S1 and S2 presentations of the same image at the same position in repetition trials. For each S1 and S2 visual field position combination (e.g. S1 8 contralateral_S2 6 ipsilateral), we selected those units that showed a significant excitatory response, with respect to baseline activity, to the stimulus presented at the S2 visual field position (e.g. 6 ipsilateral) as either S1 or S2. Note that except for repetition trials in which S1 and S2 stimuli were shown at the center position, the S1 and S2 responses originated from different trials since S2 followed a S1 presented at a different position (e.g. when S2 was presented at 6° ipsilateral, S1 could be presented at either 8 or 16° contralateral, but not at 6° ipsilateral (Figure 1C, top)). A unit was selected when either of the two tests was significant. Testing was done with two-sided Wilcoxon signed rank tests ($p < 0.05$) using only the trials of the particular S1 and S2 condition that was employed to compare the responses (i.e. compute indices; see below). The testing was performed

separately for the A and B stimuli. Using this procedure for selecting units to examine RS, we treated responses to S1 and S2 equally, avoiding biasing for S1 and, thus, for RS. Indeed, if we had selected units based solely on the responses to S1, we could have excluded from the analysis those units that showed a stronger response with stimulus repetition (repetition enhancement, (Vogels 2016)). Note that the employed procedure resulted in slightly different numbers of selected units for different S1 and S2 visual field position combinations.

When examining stimulus-selective adaptation we compared the responses to a stimulus presented as S2 in repetition (e.g. AA) and alternation (e.g. BA) trials, for each possible S1 and S2 visual field position combination. For bias-free selection of units for this comparison, we selected units by testing the significance of the response in the same 2 conditions described above, i.e. the S1 and S2 positions in repetition trials. In addition, we selected also those units that showed a significant excitatory response to the stimulus presented as S2 in alternation trials for the same S1_S2 position combination. Units that showed a significant excitatory response in at least one of these three conditions were selected. The testing was performed for AA-BA and BB-AB combinations separately.

All further analyses employed baseline-subtracted, net responses. The baseline activity was defined as the mean firing rate in a 100 ms long interval that ended at the onset of the adapter, averaged across all conditions. Using the net responses, we computed two indices to compare quantitatively net responses between stimulus conditions. The first index, the adaptation contrast index (ACI), contrasted the net responses to an image presented as S1 and S2 in repetition trials:

$$ACI = (net\ response\ S1 - net\ response\ S2) / (|net\ response\ S1| + |net\ response\ S2|).$$

We computed ACI for all A and B cases that were selected using the significance testing procedure for responses to assess RS in an unbiased way (see above).

The second index, the stimulus-selective adaptation contrast index (SSACI), contrasted the responses to S2 presented at the same position during repetition and alternation trials:

$$SSACI = (net\ response\ S2_alternation\ trials - net\ response\ S2_repetition\ trials) / (|net\ response\ S2_alternation\ trials| + |net\ response\ S2_repetition\ trials|).$$

The position of S1 was the same during repetition and alternation trials, but could differ in position from the S2 stimulus of the same trial. The index was computed for all cases that were selected using the above described significance testing procedure for responses to assess stimulus-selective adaptation.

Both indices could range between -1 and 1, with positive indices indicating RS (ACI) or stimulus-selective adaptation (SSACI). SSACI was computed for three analysis windows: the standard 300 ms [50,350] window, and two 100 ms long windows: T1 [50,150] and T2 [150,250]. The latter two windows were chosen based on the population PSTHs of all units and positions. They captured the transient, peak response phase (T1) and a later more sustained phase (T2), which shows strong RS (Liu et al. 2009). Statistical significance of the indices (median index value different from zero) was assessed with a two-sided sign test. This rather conservative test considers only the sign of the differences between S1 and S2 responses of a unit. Unlike the Wilcoxon signed rank test, it does not assume that the data come from a continuous distribution symmetric about its median, which cannot be guaranteed for adaptation indices. To avoid overestimation of the degrees of freedom of the statistical test, because of possible within-unit statistical dependencies, we averaged indices of the A and B stimuli when these were computed for the same unit before running the

statistical tests. Thus, the number of observations of the statistical test equaled the number of units for which we had indices. When testing the significance of indices for multiple adapter positions for a particular test position, we corrected the p values for multiple comparisons using the False Discovery Rate (FDR) procedure of (Benjamini and Hochberg 1995), and report the FDR corrected p value (q value).

We computed PSTHs for each neuron and condition by averaging the net, baseline-subtracted, firing rate in sliding windows of 20 ms, with a step size of 5 ms. As when computing the indices, the baseline activity was averaged across all conditions. Population PSTHs were created by averaging the normalized net firing rate across neurons per condition. Normalization was performed per neuron by dividing the net firing rate by the maximum firing rate in 20 ms sliding windows, with a step size of 5 ms, across all stimulus conditions presented to the unit.

We show standard errors of the mean normalized responses to S1 and S2, reflecting unit-to-unit variability in response, in the figures picturing PSTHs. We computed 95% bootstrap confidence intervals of the median adaptation indices with the bias corrected and accelerated percentile method ("bootci" function of Matlab; 2000 resamplings). We performed statistical tests on the data pooled across monkeys and on individual monkey data. The statistical test outcomes in the figures are for the pooled data. Except when noted, the effects of the pooled data reflected the trends observed in each monkey.

Results

We examined the spatial specificity of repetition suppression of MUA of IT neurons in two monkeys. We recorded 417 units (243 in monkey M1) in 50 S probe and 4 single electrode penetrations, of which 365 units (203 in M1) passed the offline stability tests (see Materials and Methods). We searched for visual responses using a set of 50 complex images. Based on the MUA of the simultaneously recorded channels, we selected two images (A, B) that were employed in the subsequent adaptation test. In the adaptation test, we presented during passive fixation A or B at one of 8 possible visual field positions (S1) which was followed, after a delay of 400 ms, by one of the two images (S2) at the same or a different position (Figure 1). We employed two different images, A and B, to be able to examine stimulus-selective adaptation. The identity of the image was unpredictable since S1 or S2 could be either A or B, and half of the trials were repetitions (AA, BB) and the other half alternations (AB, BA).

RF and time course of responses.

Three hundred twenty-six units (179 in M1) showed a significant visual response to S1 for at least one of the positions (see Materials and Methods for statistical testing procedures). Figure 2A shows the mean response of these 326 units to the effective stimulus A at the different positions. The pattern of the S1 responses for the different positions agreed with previously reported RF maps of single IT neurons (Op De Beeck and Vogels 2000). First, we observed in each monkey the strongest S1 response, averaged across units, at the foveal position (Figure 2A). Pooled across monkeys, 48% of the units showed the largest response there. This outcome agrees very well, despite the coarser spatial sampling and use of MUA in the present study, with a previous IT RF mapping (Op De Beeck and Vogels 2000), whom reported that 51% of their single IT neurons had a maximal response at

the fovea. The large majority of units (78%) showed a significant response at the foveal position, with a median net firing rate of 14.9 spikes/s. Second, although decreasing with eccentricity, responses were present, on average, at each of the visual field positions (Figure 2A). This includes the presentation of the stimulus at 6° in the ipsilateral visual field, to which 53% of the units showed a significant response (Supplemental Table 1; see https://github.com/FabFra/Receptive-Field_-Repetition-Suppression). Third, responses were, on average, stronger in the contralateral than in the ipsilateral visual field: mean responses were smaller at 6° ipsilateral compared to 8° contralateral (Figure 2A), despite the higher eccentricity of the latter position.

The sparse sampling of positions hindered our ability to quantify the RF size of the units. Nonetheless, to have an estimate of the distribution of the minimal extent of the RF in the horizontal and vertical dimension, we computed the number of units that showed a significant (greater than baseline) response to S1 at each of two horizontal or vertical positions. These data were then plotted as a function of the distance between the two positions. Supplemental Figure S1 (see https://github.com/FabFra/Receptive-Field_-Repetition-Suppression) shows the percentage of units with a minimal RF width at the horizontal or vertical dimension. For the pooled data, the median minimal extent was 14° and 12° for the horizontal and vertical dimension, respectively. The RF extents were smaller for monkey M2 than M1.

Combined lesion-recording studies showed that ipsilateral IT responses originate from transcallosal input from the other hemisphere (Gross et al. 1977; Rocha-Miranda et al. 1975). Thus, we surmised that ipsilateral responses have a longer response latency than those at similar or even greater eccentricities in the contralateral visual field. As far as we

know, previous studies of IT RFs did not examine the time course of the responses at different positions. To compare the time course of the S1 response amongst the different positions, we normalized each of the population PSTHs of Figure 2A by their peak response. The resulting normalized PSTHs are shown in Figure 2B (red), and for comparison, we replotted at each position the normalized PSTH of the foveal position (blue). Several points about the time course of the responses are noteworthy. First, the responses at the foveal position were more sustained than those at the far peripheral positions: the latter PSTHs showed a deeper dip around 200 ms post-stimulus onset. Second, the response latencies at the foveal and contralateral positions were very similar, while the peak response latency was clearly longer at the ipsilateral position. To quantify the difference in the response time course between the foveal and the other positions, we shifted the normalized PSTH of each peripheral position in small time-steps and computed for each time-step the root mean squared error (RMSE) of the difference between the foveal and the shifted PSTH (interval of 0-300 ms post-stimulus onset; step size 5 ms). The shift having the minimum RMSE defined the difference in latency between the time courses of the foveal and peripheral position, and these are indicated next to the corresponding PSTHs in Figure 2B. This analysis showed that the responses at the ipsilateral position lagged those at the foveal and other peripheral positions by 20 ms. Note that this latency shift for the 6° ipsilateral position was markedly larger than that for the more peripheral 16° contralateral position (only 5 ms lag; Figure 2B), despite the weaker response at the 16° position (Figure 2A). The longer latency of ipsilateral responses agrees with studies showing their transcallosal origin (Gross et al. 1977; Rocha-Miranda et al. 1975).

Spatial generalization of repetition suppression.

Our adaptation test included trials in which S2 was at the foveal position and trials in which S2 was presented at peripheral positions (Figure 1). First, we will describe the responses to the foveal S2 as a function of the position of the preceding S1 in repetition trials (AA or BB). For this analysis, we selected those cases for which there was a significant response to either A or B when that stimulus was presented as S1 or as S2 at the foveal position in repetition trials (AA or BB; see Materials and Methods). This selection procedure avoided a biased assessment of RS that could have occurred when testing only responses to S1 and thus missing units that showed only a significant response to S2 (i.e. strong repetition enhancement). Figure 3A&C shows the PSTHs of the S2 responses, split up for the different preceding S1 positions. For comparison, we also plot the population PSTHs of the responses to the same images when these were presented foveally as S1. Because of the statistical testing procedure, which was performed separately per S1 visual field position and resulted in incompletely overlapping samples, the responses to S1 differed slightly amongst the different conditions. Replicating previous work (Vogels 2016), repetition of the same image at the same position resulted in marked RS of IT spiking activity. The median Adaptation Contrast Index (ACI; see Materials and Methods) when S1 and S2 were presented both at the foveal position was 0.3, pooled across monkeys (Figure 3B&D), which corresponds to approximately a 50% reduction in net response with repetition. RS was greater in M1 (median ACI = 0.30; n= 160) than in M2 (0.26; n = 88). RS was reduced but still present for each of the 7 peripheral adapter positions for the data pooled across monkeys (all median ACIs in Figure 3B&D were significantly different from 0 (FDR corrected p values (sign test))). When the adapter was at an eccentricity of 6 to 8°, median ACIs were about 0.11, which corresponds to a 20% response reduction. RS was present in each monkey for the ipsilateral positioned adapter (median ACI = 0.09; 16% response reduction; M1: 0.10; M2: 0.06). When

the adapter was at the relatively far eccentricities of 12 and 16°, median ACIs were around 0.06 (11% response reduction) in M1, but were only 0.01-0.02 in M2. The difference in the degree of spatial generalization of RS between the monkeys fits their difference in RF extent (Supplemental Figure 1).

The above analyses assume that nearby recording sites provide an independent measure of RS. We tested this directly by assessing whether the difference in the degree of RS for a pair of sites depended on the distance between the sites. When the MUA of neighboring recording sites overlap, one would expect that ACIs would be more similar for neighboring sites than for sites that are more distant to each other. Hence, for each electrode penetration, we computed the absolute difference in ACI for all possible pairs of recording sites of the penetration, thus obtaining differences in ACI for different inter-site differences along the electrode shaft. We performed this analysis for all S1-S2 position combinations where S2 was presented at the center during repetition trials. Supplemental Figure 2 (see https://github.com/FabFra/Receptive-Field_-Repetition-Suppression) shows the median difference in ACI as a function of inter-site distance for each examined S1-S2 position combination. We did not observe a trend for smaller median differences in ACI for nearby compared to distant sites, which argues against a putative spillover of activity between nearby sites having an effect on our RS data.

The adaptation test also included trials in which S2 was presented at peripheral positions that differed from the S1 position (Figure 1). In these trials, both adapter and test stimuli were presented at peripheral positions with an eccentricity ranging between 6 and 16°, with the distance between the two stimuli ranging between 8 and 22°. The population PSTHs of the S2 responses in the peripheral S2 conditions and the corresponding S1

responses, together with the distributions of the ACI, are shown in Figure 4. Statistically significant RS was present for the peripheral test positions when pooling the data of the two monkeys, with median ACIs ranging between 0.06 (11% response reduction) and 0.11 (20% reduction). For the pooled data, significant RS was observed even for the largest tested distance of 22° between adapter and test positions (dashed red box in Figure 4). However, for the distances of 18 to 22°, RS was present in M1, but it was small to absent in M2, which is likely because of the smaller RFs in this animal (Supplemental Figure 1).

We included conditions in which adapter and test stimuli were positioned in different hemifields, thus testing whether adaptation transfers across hemifields. Adapting to an 8° contralateral positioned adapter reduced the response to an ipsilateral test stimulus in both animals (median ACI: M1: 0.16; M2: 0.06), which implies generalization of RS across hemifields for a distance of 14°. We take this wide extent of cross-hemifield transfer as evidence that RS originates at least partially in IT.

Figure 5 shows the median ACI (and bootstrapped 95% confidence intervals) as a function of the distance between adapter and test stimuli for the foveal (Figure 5A) and peripheral (Figure 5B) test positions. It is clear that the strongest RS was present when adapter and test stimuli were presented at the same (foveal) position. The degree of RS decreased strongly when adapter and test stimuli became spatially separated, with small but still significant suppression for distances of 12 for a foveal test stimulus (Figure 5A). Within each peripheral test position, far distances resulted systematically in smaller ACIs than the smaller distance (Figure 5B). Note that having adapter and test stimuli in different hemifields with a distance of 14° resulted in RS that was overall similar in magnitude to that obtained when adapter and test stimuli were in the upper versus the lower visual field with a distance

of 12° (encircled data points in Figure 5B). This shows that across-hemifield adaptation can be of similar strength to within-hemifield adaptation for similar adapter-test distances.

Spatial generalization of stimulus-selective adaptation.

For each adapter-test position combination, the adaptation test included repetition (AA or BB) and alternation (BA and AB) trials. Based on previous studies (Vogels 2016), we expected to observe stimulus-selective adaptation, i.e. a greater suppression in repetition than in alternation trials. To assess this, we selected for responsive units in an unbiased way, by testing whether there was a response to an image presented as S1 or S2 in repetition trials, or as S2 in alternation trials. This selection was performed separately for A and B. As expected, responses were significantly lower in repetition compared to alternation trials when the adapter and test stimuli were both at the foveal position (Figure 6). To quantify stimulus-selective adaptation for each unit, we computed the stimulus-selective adaptation contrast index (SSACI; see Materials and Methods), which compares the responses to the same image presented as S2 in repetition and alternation trials. Positive values indicate stimulus-selective adaptation. The median SSACI when S1 and S2 were presented at the same (foveal) position was 0.22 (M1: 0.23; M2: 0.14), which corresponds to a 36% lower response in repetition compared with alternation trials. Note that the median SSACI was lower than the median ACI, because IT neurons can show cross-adaptation, i.e. a reduced response to S2 in alternation trials, when compared with the same image presented as an adapter (De Baene and Vogels 2010; Sawamura et al. 2006). However, typically, as also observed here, the cross-adaptation is smaller than the adaptation effect in repetition trials (De Baene and Vogels 2010; Sawamura et al. 2006). Next, we asked to what extent stimulus-selective adaptation generalized across position by examining it for the different adapter-

test position combinations. Note that stimulus-selective adaptation is important to assess because it also acts as a control for stimulus identity-specific order effects (e.g. a general reduced response during the course of a trial).

When S2 was at the foveal position and the adapter in the periphery, stimulus-selective adaptation was statistically significant for the 6-8° adapter eccentricities (Figure 6), including the ipsilateral position. For larger adapter eccentricities, the median SSACI was marginally significant (16° contralateral) or failed to reach significance (12° on the vertical meridian) for the pooled data. One potential explanation for the weak stimulus-selective adaptation at the higher adapter eccentricities is that the units simply were unable to differentiate the images at these high eccentricities. We tested this possibility directly by testing for each of the selected units whether their responses to A and B, presented as S1, differed significantly (Wilcoxon Rank Sum test; $\alpha = 0.05$). For each of these high eccentricities, the percentage of units showing a significant response difference between A and B was significantly larger than 5%, the Type 1 error of the statistical test (15% ($p = 0.00001$), 16% ($p = 0.00001$) and 25% ($p = 0.00001$) units for 16°, 12° above and 12° below, respectively; Chi Square goodness of fit test). Hence, the weak stimulus-selective adaptation at the higher eccentricities cannot be explained by a loss of stimulus selectivity at these eccentricities.

Next, we examined the time course of the stimulus-selective adaptation effect. To do this, we subtracted for each unit the normalized responses to S2 in repetition trials from that in alternation trials in bins of 20 ms, with a step of 5 ms, and averaged the difference across units. The time course of the mean response difference (and bootstrapped 95% confidence intervals; 1000 resamplings) is shown in Figure 6C for each of the adapter positions, together

with the net response to S2 for comparison. In the case of the foveal adapter and test stimulus, the stimulus-selective adaptation started during the rising phase of the response and reached its maximum approximately 200 ms after stimulus onset, in agreement with a previous report (Liu et al. 2009). For the 8° contralateral, 6° vertical meridian and 6° ipsilateral adapter conditions, reliable stimulus-selective adaptation started at the response peak or later. Also, note that this was due to a dip around 200 ms in the response to the test stimulus in repetition trials. Because stimulus-selective adaptation peaked quite late during the course of the response, we re-computed the SSACI indices for a later, shorter window (T2, [150,250]; see Materials and Methods), capturing the later phase of the response that showed stronger RS. The median SSACIs (and 95% confidence intervals) computed for the full-time window and for T2 are shown in Figure 7A. Stimulus-selective adaptation was consistently stronger in the second time window. For that time window, adaptation was present when the distance between the adapter and the foveal test stimulus was up to 12°.

Figures 8 shows the stimulus-selective adaptation for the conditions in which the S2 stimulus was at peripheral positions. For each of the 8 conditions, the SSACI, computed for the full 300 ms window, was larger than zero, typically around 0.05 (10% response difference), with 6 conditions reaching statistical significance with the sign test when pooling the monkeys. However, in these 6 conditions, stimulus-selective adaptation was convincing (and significant) only for the data of M1 (Figure 8B). Inspection of the PSTHs suggested that, also in this case, the stimulus-selective adaptation was most prominent in the second half of the response and much less for the transient peak response. Thus, computing the SSACI using the 300 ms analysis window may have underestimated it. To address this, we computed SSACI for two shorter analysis windows: an early window (T1, [50,150]; see

Materials and Methods), capturing the peak response, and the late window (T2, [150,250]). The median SSACIs (with 95% confidence intervals; pooled across monkeys) for these two windows for each of the peripheral S2 conditions are shown in Figure 8C. Except for the condition with the largest distance (22°) between adapter and test stimulus, the SSACIs were markedly greater for the late compared with the early window. All confidence intervals, except that for the 22° distance condition, did not overlap with zero for the late window, with median SSACIs ranging between 0.1 and 0.25 (also see Figure 7B, where the median SSACIs are plotted as a function of S1-S2 distance). Noteworthy is that we observed stimulus-selective adaptation in this late analysis window for distances between adapter and test stimuli up to 18° (dashed red boxes in Figure 8A). Furthermore, when the adapter was positioned at 6° in the ipsilateral field and the test stimulus at 8° contralateral, the median SSACI for the late window was 0.20, indicating profound stimulus-selective adaptation by the ipsilateral adapter having a distance of 14° from the contralateral test stimulus. As for the foveal S2 conditions, the SSACIs for a particular S2 position tended to be higher when adapter and test stimuli were closer (Figure 7B).

Repetition suppression does not equal expectation suppression

In our experimental design, the identity, A or B, of the test stimulus could not be predicted from the adapter stimulus. Hence, the presence of stimulus-selective adaptation effects for (some of) the peripheral adapters, including the ipsilateral S1, rules out that the observed response suppression resulted solely from expectation of the test position in our experimental design, i.e. expectation suppression following statistical learning of adapter-test position transitional probabilities (Meyer and Olson 2011). To obtain an estimate of the effect size of a potential expectation suppression, we included a condition in our design in

which the S1 stimulus was a white square presented at 16° ipsilateral, followed by the presentation of the stimulus, A or B, at the center or at 16° contralateral. Transitional probabilities for the adapter-test positions in this condition were identical to those of the other adaptation conditions. However, no significant response reduction was observed for the foveal S2 when this followed the peripheral square (median ACI = 0.02; $p = 0.09$; Figure 6E; data pooled across monkeys), suggesting a negligible, if any, contribution of statistical learning effects to the observed RS. Furthermore, the small, but insignificant reduction in S2 response after the peripheral square presentation may have resulted from cross-adaptation, because, contrary to our expectation, the averaged MUA showed small, long latency responses to that stimulus (mainly in M1; Figure 6E).

Stimulus-selective adaptation without excitatory responses to the adapter.

An obvious explanation of the reduction of RS with increasing eccentricity of the adapter stimulus (Figure 5A) is that responses to the adapter stimulus decrease with increasing eccentricity. For instance, only 41% (M1: 50%; M2: 30%) of the units showed a significant response to S1 at the 16° contralateral position (compared to 78% for the foveal position; Supplemental Table 1). To assess whether the difference in RS amongst the S1 positions can be explained by the response strength to the adapter, we plotted the ACIs for the responsive unit and image combinations as a function of the normalized net response to the adapter of that unit. To assess the influence of adapter response strength on the test response, we fixed the test position, and thus only the conditions with S2 at the foveal position were included in this analysis. The net responses to the adapter were normalized by the maximum net response to the same image across the 8 different S1 positions. As before, all units that responded significantly to the image (A or B) presented as S1 at the foveal

position or as S2 in repetition trials were included, thus avoiding a biased ACI. Also, the units
 needed to have an excitatory net response to at least one of the 8 S1 positions. For the
 selected 476 cases (resulting in $8 \times 476 = 3808$ data), Figure 9A shows the median ACI (and
 95% confidence interval) computed for bins having a size of 0.1 normalized response (Figure
 9A, red). We plotted only the data with a normalized adapter response larger than -0.3,
 since the confidence intervals for the data with a smaller normalized response (8% of the
 data) were extremely large because of the relatively small number of cases. The ACI
 decreased with weaker adapter responses (Spearman rank correlation $R = 0.13$; $p = 2.58 \times 10^{-13}$; $n = 3027$ cases for which the normalized response was equal or larger than zero).
 However, the ACI was still larger than 0 when the net response to the adapter was close to
 zero or even negative. To appreciate this better, we pooled the ACIs for which the
 normalized net response to the adapter was between -0.3 and 0. The median ACI for this
 sample of cases ($n = 473$) in which there was a negative net response to S1 was 0.06, which
 was significantly larger than zero ($p = 1.59 \times 10^{-7}$; sign test). Figure 9B shows the population
 PSTHs of the responses in these repetition conditions and to the same image as foveal S1 in
 the same units for comparison. Note the consistently smaller response to S2 than S1.
 However, an early weak excitatory response followed by a stronger longer lasting inhibition
 was notable in the PSTH of the adapter. To address the possibility that the remaining early
 excitatory responses caused RS, we excluded those cases for which there was an excitatory
 response in the T1 analysis window ([50,150]). This eliminated the excitatory response to S1
 (Figure 9E) but not the RS: the median ACI for this set of cases was 0.08 ($p = 3.37 \times 10^{-08}$; $n =$
 226).

As a control, we performed the same analysis for the responses in alternation trials. We employed the same unbiased selection procedure by including unit-image combinations for which there was a significant response to the image presented at the foveal position as S1 or as S2 when it followed the other image as adapter, i.e. in alternation trials. We computed ACI by comparing the responses to the same image presented as S1 and as S2 in the alternation trials. Normalized net responses for S1 were computed by division by the maximum net response to A or B, across the 8 adapter positions. As expected from stimulus-selective adaptation, the median ACIs for the alternation trials were below those for the repetition trials (Figure 9A). Importantly, this was also the case when the normalized net responses for the adapter were close to zero. In fact, the median ACI in the alternation trials for adapter responses between -0.3 and 0 was only 0.01, which did not differ significantly from zero ($p = 0.16$; $n = 631$; Figure 9C) and was significantly lower than the median ACI in repetition trials (Wilcoxon rank sum test; $p = 0.02$). For each monkey, the median ACI for alternation trials (M1: 0.02, $p = 0.09$; M2: 0.003, $p = 0.82$) was lower than that for repetition trials (M1: 0.089, $p = 3.29 \times 10^{-6}$; M2: 0.048, $p = 0.006$) for the adapter net responses between -0.3 and 0. We also computed the ACI for the alternation trials for the cases in which the net response in the T1 window was negative. For those 318 cases, the median ACI was 0.01 ($p = 0.3$), which was significantly lower than that for the repetition trials (Wilcoxon rank sum test; $p = 0.003$).

These data suggest that stimulus-selective adaptation can occur in IT without measurable excitation of the units by the adapter. In order to examine the variability of the time course of this adaptation effect, we resampled the cases, with replacement, for the repetition and alternation conditions, and then computed the median ACI for each

resampling and subtracted the median ACI for the repetition trials from that for the alternation trials. The ACIs and difference scores were computed using sliding windows of 100 ms duration, with a step of 10 ms. This long window duration was chosen to avoid noisy time courses (the adaptation effect was rather small). The difference score was computed for each of the 1000 resamplings. Figure 9D and 9G shows the difference score for the original data (and the 95% confidence intervals), computed using the above described bootstrapping procedure, for the selected set of cases with normalized net responses between -0.3 and 0 and the cases for which in addition there was no excitatory response in the T1 window, respectively. For both sets, the stimulus-selective adaptation occurred relatively late, around 200 ms post-stimulus onset. This late onset compares well with the time course of the stimulus-selective adaptation we observed when considering all units, including those producing a clear response to the adapter stimulus (Figure 6C and 7A).

Discussion

We observed RS of macaque IT spiking activity when adapter and test stimuli are presented at different positions in the visual field, for distances between adapter and test stimuli up to 22°. RS was also present when adapter and test stimuli were presented in different hemifields. Stimulus-selective adaptation was the strongest around 200 ms after test stimulus onset. In this late period of the response, stimulus-selective adaptation was reliable for distances between adapter and test stimuli up to 18° and was present when adapter and test stimuli were presented in different hemifields. Surprisingly, we found late stimulus-selective adaptation, albeit small, even when there was no noticeable response to the adapter. These data suggest that RS at least partially originates within the IT circuit or reflects feedback from downstream areas.

Contribution of upstream extrastriate areas to adaptation in IT.

The ventral bank of the rostral STS obtains its main input from posterior IT (TEO/PIT; (Kravitz et al. 2013)), where RFs are smaller (Boussaoud et al. 1991; Hikosaka 1998; Yasuda et al. 2010) than in anterior IT. However, it is also connected to the Fundus of the Superior Temporal (FST) area (Boussaoud et al. 1990; Kravitz et al. 2013), which has large RFs that can cross into the ipsilateral field (Desimone and Ungerleider 1986; Hikosaka 1998). Several arguments, however, argue against FST as being a major driver of the spatial generalization of RS in IT. First, adaptation with long-duration adapters is highly position specific in MT (Kohn and Movshon 2003) and is directly or indirectly inherited from V1 (Patterson et al. 2014). Since FST receives strong, direct input from dorsal stream area MT (Desimone and Ungerleider 1986), it is likely that adaptation in FST is inherited from MT and V1 and thus spatially specific, unlike what we observed in IT. We should note that brief adaptation reduces the brief transient response to motion onset and this short-lasting effect generalizes across position within the MT RF (Priebe et al. 2002), but this adaptation effect is very different in the time domain from the one we observed in IT, which affects strongly the late sustained response phase. Second, no object-selective fMRI adaptation for similarly sized stimuli as employed in the present study was observed in FST (Sawamura et al. 2005), but was present along the ventral bank of the STS in that monkey fMRI study. FST, however, does show strong motion direction selective fMRI adaptation (Nelissen et al. 2006).

The present study suggests that at least part of RS is not inherited from upstream areas. In fact, although unlikely, it cannot be excluded that stimulus-selective adaptation is not inherited at all from upstream areas. Previously, we showed that RS is partially position specific using smaller distances along the vertical meridian (De Baene and Vogels 2010;

Kuravi and Vogels 2017). However, the increase in RS when adapter and test stimuli overlap compared to when there is no overlap does not need to result from inheritance of adaptation in upstream areas with small RFs. Indeed, it can result from adaptation within IT of position-specific input to the neuron, for instance by synaptic depression of position-specific afferents of the IT neuron. Basically, this is the same mechanism that may underlie stimulus-selective adaptation for stimuli that produce an equal response in a neuron (Sawamura et al. 2006).

Spatial generalization of adaptation of IT neurons.

RS at the foveal position was much stronger when adapter and test stimuli overlapped than when adapting at peripheral positions. Indeed, when the adapter was at large eccentricities (12 to 16°), the decrease in response was subtle. Previous studies (De Baene and Vogels 2010; Kuravi and Vogels 2017) found that RS was smaller when adapter and test stimuli were at non-overlapping compared to overlapping peripheral positions. This suggests that the spatial distance between adapter and test stimuli is one factor that contributes to the reduced RS at large adapter eccentricities. Other possible factors are that not all IT units have RFs that span the tested peripheral positions and that their responses typically decrease with increasing eccentricity (Op De Beeck and Vogels 2000). This is supported by the drop in RS with decreasing response to the adapter (Figure 9) and the broader spatial generalization in M1, which had larger RFs, compared to M2. Because of the use of MUA, the presence of responses at different positions cannot guarantee that the same single neuron shows a response at those positions. This may explain why including only units that showed a significant response to the adapter stimulus at a particular position did not markedly increase the degree of RS (data not shown). Because of the multiple factors

that can codetermine the degree of adaptation at different peripheral positions, we concentrated in this work on examining the presence of RS (and stimulus-selective adaptation) for the different adapter-test conditions and not on the comparison of the degree of RS between adapter positions.

The stimulus selectivity of the adaptation effect (i.e. response difference between test stimuli following different adapters) appears to generalize less across spatial position than RS (i.e. suppressed responses to test compared to adapter). Indeed, stimulus-selective adaptation was weak to absent for far peripheral adapter positions and this could not be attributed to a loss in image selectivity at these positions. RS was, although still statistically significant, also markedly reduced for the far peripheral adapters. The combination of cross-adaptation in the alternation trials, a weak suppression in repetition trials at large distances between adapter and test stimuli, and reduced responses for the peripheral adapters can explain the weak to absent stimulus-selective adaptation for the far positions. Note that the adapter and test images could differ in their effectiveness in driving the neuron. For instance, the adapter (e.g. A) could be more effective than the following test image (B), which can increase cross-adaptation and thus reduce stimulus-selective adaptation in general (De Baene and Vogels 2010).

Adaptation in IT crosses hemifields.

The longer latency of ipsilateral responses in IT we observed (Figure 2) agrees with seminal split-brain recording studies (Gross et al. 1977; Rocha-Miranda et al. 1975) that showed a trans-callosal origin of the ipsilateral input to IT. We report here for the first time that stimulus-selective adaptation of macaque IT units generalizes across hemifields, i.e.

when adapter and test stimuli are initially processed in different hemispheres. We believe this is strong evidence that at least part of the adaptation originates within IT, since upstream areas of the ventral visual pathway have a narrow ipsilateral representation.

Our macaque IT data agree with some but not all human fMRI studies that examined the cross-hemifield transfer of adaptation in ventral stream areas. Indeed, these adaptation fMRI studies reported no (McKyton and Zohary 2007), partial (MacEvoy and Epstein 2007) to full transfer of adaptation (Kovacs et al. 2012) across hemifields in the Lateral Occipital Complex. Full transfer of fMRI adaptation across hemifields was observed for faces also in the fusiform face area (Kovacs et al. 2012; Kovács et al. 2008). Why these fMRI studies differed in outcome is unclear and because of methodological differences difficult to pinpoint.

A model of stimulus-selective adaptation in IT

What mechanisms underlie stimulus-selective adaptation in IT? Our previous optogenetic study suggests that firing rate dependent fatigue plays only a minor, if any, role in RS in IT (Fabbrini et al. 2019). A possible feedforward, local processing model of stimulus-selective adaptation in IT, that explains the current as well as previous findings (Kaliukhovich and Vogels 2016; Vogels 2016), starts from the observation that neurons in IT receive position- and feature-specific inputs from upstream areas, which underlies their position (Op De Beeck and Vogels 2000) and feature selectivity (Tanaka 1996). In the model, IT neurons with similar feature selectivity form interconnected feature assemblies (Fujita and Fujita 1996), consisting of circuits of excitatory pyramidal neurons and inhibitory interneurons that process these features. We assume that the presentation of a stimulus will

produce reduced activity (because of e.g. synaptic depression) of the stimulated IT afferents. Also, we assume that it activates a short-term plasticity mechanism in the pyramidal-interneuron circuit of the assembly that will result in suppressed activity of the neurons when the stimulus is repeated. Recent work in rodents provided evidence for adaptation-induced changes in excitatory-inhibitory circuits in the auditory cortex (Natan et al. 2015; Natan et al. 2017). Such, still poorly understood, circuit effects may contribute to the stimulus-selective adaptation in macaque IT. A feature assembly receives input from upstream units with different RFs, and, hence, will be activated by stimuli at different positions. Therefore, activation of the adaptation mechanisms within a feature assembly can result in a reduced response to a test stimulus presented at different positions than the adapter. The extent of the spatial generalization of adaptation will depend on the RF of the feature assembly, which results from pooling the RFs of the input units. In addition, we postulate that it depends on the connectivity between IT units of the same feature assembly that have partially overlapping RFs. The latter explains that weak adaptation was still present in units that were not excited by the stimulus at the adapter position (Figure 9). That IT neurons can receive input from outside their “classical” RF agrees with work that shows that IT neurons can receive excitatory input from part of the visual field that is inhibited by other neurons, which was revealed by blocking GABA receptors (Wang et al. 2002).

The bulk of stimulus-selective adaptation occurred relatively late in the response, especially when adapter and test stimuli were spatially segregated. The mechanistic origin of the late stimulus-selective adaptation is not clear yet. One plausible option is that, being based on recurrent activity in the excitatory-inhibitory circuits within and between the

assemblies, it takes more time to develop, compared to the early phase of the response which is likely driven mostly by feedforward connections (Lamme and Roelfsema 2000),

The model consists of different assemblies for different features and their feature specificity explains why adaptation is stimulus selective. In line with other studies (Kaliukhovich and Vogels 2016; Zoccolan et al. 2005), we assume that the response of a unit in a feature assembly is normalized by the response of units of the same and other feature assemblies. This explains the finding that adapting to an ineffective stimulus, which reduces the divisive normalizing response, enhances the response to the simultaneous presentation of an effective and ineffective stimulus (Kaliukhovich and Vogels 2016). Since the engagement of the adaptation circuit likely involves a rather specific activation of the units, a specific “brute force” excitation of the neurons is unlikely to result in adaptation, as we observed before when optogenetically activating a (small) population of IT neurons (Fabbrini et al. 2019).

Repetition suppression and top-down modulations.

The above described model assumes that stimulus-selective adaptation originates within the IT circuit. However, it is possible that part of RS in IT results from feedback from downstream areas. It has been suggested that RS results from the fulfillment of an expectation of repetition, reflecting a reduced prediction error. Evidence for this hypothesis is based on human fMRI studies that showed reduced adaptation in blocks with a high probability of alternation trials compared to blocks with a high probability of repetition trials (Grotheer and Kovács 2016; Kovacs and Vogels 2014; Summerfield et al. 2008). Interestingly, the repetition probability effect on fMRI adaptation is equal when adapter and test stimuli

are presented in the same or in opposite hemifields (Kovacs et al. 2012). However, repetition probability effects on fMRI adaptation can depend on stimulus category or even be absent (Kovacs et al. 2013; Olkkonen et al. 2017). Furthermore, it was not found in macaque IT at the spiking activity and local field potential level (Kaliukhovich and Vogels 2011), even when the monkeys' behavior was affected by repetition probability (Vinken et al. 2018).

The absence of a repetition probability effect does not rule out that RS depends on feedback from downstream areas (Friston 2005; Henson 2016). In fact, human fMRI dynamic causal modeling (DCM) studies suggested changes in top-down connectivity amongst body and face-category selective areas with RS for bodies (Ewbank et al. 2011) and faces (Ewbank et al. 2013), respectively. Interestingly, these changes in the DCM top-down connectivity were evident when the faces or bodies differed in size or viewpoint during repetitions of the same identity but not for equal size and viewpoint repetitions. Such inter-areal recurrent processing changes may have contributed to the stimulus-selective adaptation in macaque IT when adapter and test position differs. This may explain the late onset of the stimulus-selective adaptation in our study when adapter and test stimulus differed. However, the nature of these inter-areal changes in connectivity is not understood and depends on the ability of dynamic causal modeling of the slow BOLD signals to capture inter-areal processing that operates on much faster time scales.

Conclusion

RS in macaque IT shows generalization across relatively large distances between adapter and test stimuli and when these stimuli are presented in different hemifields. This suggests that at least part of RS is not inherited from upstream ventral stream areas with

826 smaller RFs. The relatively late stimulus-selective adaptation that tolerates a spatial offset
827 between adapter and test stimuli may reflect recurrent intracortical processing within IT or
828 top-down influences from downstream areas. Further studies using simultaneous recordings
829 in IT, upstream, and downstream areas, complemented by causal manipulations of activity in
830 the latter areas, may produce insights into the respective contributions of inheritance,
831 processing within IT and top-down modulations.

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840 The authors declare no conflict of interests, financial or otherwise.

841 **Author Contributions**

842 F.F. and R.V. designed the study. F.F. performed the experiments, analyzed the data and
843 prepared the figures under the supervision of R.V.. F.F. and R.V. wrote the manuscript.

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Figure Captions

Figure 1. Experimental design and stimulus conditions. **A.** The maximum vertical or horizontal extent of the images was 3° of visual angle. On each trial, monkeys were required to fixate a small red square shown at the center of the display. After fixation of the square for 500 ms, a visual stimulus (S1, adapter) was presented for 300 ms, followed by an interstimulus interval of 400 ms, after which a second visual stimulus (S2, test) was presented for 300 ms. To complete the trial and obtain a fluid reward, monkeys had to additionally maintain their fixation for 500 ms after S2 offset. On each recording session, two stimuli, A and B, were selected based on the MUA responses. On repetition trials, S1 and S2 were identical (A-A or B-B), while on alternation trials, S1 and S2 were different (A-B or B-A). The positions of S1 and S2 were manipulated independently. **B.** On each trial, S1 was presented at one of 8 different positions (left): at the center, at 8° and 16° eccentricity on the horizontal meridian in the contralateral visual field (C), at 6° and 12° eccentricity on the vertical meridian in the upper (A) and lower (B) visual field or at 6° eccentricity on the horizontal meridian in the ipsilateral visual field (I). For each S1 position, on half of the trials, S2 was presented at the center of the visual field (foveal S2, right). **C.** On the other half of the trials, S2 was presented at one of the four 6° or 8° positions, so that each of the four

1013 peripheral S2 positions could be preceded by two different S1, presented along the same
 1014 axes of the visual field.

1015

1016 **Figure 2. Effect of spatial location on S1 responses.** Population peristimulus time
1017 histograms (PSTHs; bin width 20 ms, step size 5 ms) of the responses to the effective
1018 stimulus presented as S1 at the 8 possible positions. On each PSTH, the two vertical dashed
1019 lines indicate stimulus onset and offset, respectively. Shaded bands indicate SEM. N denotes
1020 the number of units. **A.** PSTHs of normalized net firing rate. The position of each PSTH
1021 represents the position of the S1 stimulus, as indicated above each PSTH. **B.** PSTHs of the
1022 responses normalized by their peak activity, separately for each position (red). For
1023 comparison, the normalized response to the S1 stimulus at the foveal position is shown in
1024 blue. For each peripheral position, the PSTHs were shifted in small time-steps and the RMSE
1025 of the difference between the foveal and the peripheral position was computed. The shift in
1026 ms with the minimum RMSE is indicated above each PSTH. Note the larger temporal shift for
1027 6° ipsilateral.

Figure 3. Generalization of RS: foveal S2 position. The position of each PSTH and ACI distribution represents the position of the S1 stimulus, as indicated above each PSTH. N_c denotes the number of cases (number of units x stimulus (A or B) combination). N_u denotes the number of units. For each S1 position: above, population PSTHs of the normalized net responses to the presentation of a stimulus, A or B, at the foveal position, as S1 (blue), or as

1034 S2 (red) in repetition trials following the presentation of the adapter at each of the possible
1035 8 positions (indicated above each PSTH). Same conventions as in Figure 2A. Below:
1036 distributions of ACI, separated per monkey (M1, green; M2, yellow). Arrows indicate the
1037 median ACI for each monkey, and the red dashed vertical line indicates the median of the
1038 data pooled across monkeys. Statistical significance (median value different from zero) was
1039 assessed with a two-sided sign test. The q values correspond to the FDR corrected p values.

Figure 4. Generalization of RS: peripheral S2 positions. Each row shows the data for a different S1_S2 position combination, as indicated by the icons on the left. **A:** population

PSTHs of the normalized net responses to the presentation of a stimulus, A or B, as S1 (blue) or as S2 (red) in repetition trials. **B**: corresponding distributions of ACI. Same conventions as in Figure 3. The red dashed box indicates the data for the condition with the maximum distance between adapter and test stimuli.

Figure 5. Spatial generalization of RS for different distances between adapter and test stimulus. Median ACI as a function of the distance between adapter and test stimuli for the foveal (**A**) and peripheral (**B**) test positions. The circles represent the median values, the vertical lines the bootstrapped 95% confidence intervals. Each color corresponds to a different adapter position, as indicated in the legend. The right Y axis indicates the corresponding percentage value of response reduction. In **B**, the dashed lines connect the median ACI values of the two S1 positions with the same S2 position. The red dashed ellips highlights the ACI values for two conditions with an ipsilateral adapter or test position and two other conditions with similar adapter-test distances along the horizontal and the vertical meridian.

Figure 6. Stimulus-selective adaptation: foveal S2 position. A-C. Each row shows the data for a different adapter position, as indicated by the icons in the left column. S2 was

presented at the foveal position. **A.** Population PSTHs of the normalized net response to the presentation of a stimulus, A or B, at the foveal position as S2 during repetition (red) and alternation (cyan) trials. Same conventions as in Figure 3. **B.** Distributions of SSACI, separated per monkey (M1, green; M2, yellow). Same conventions as in Figure 3. **C.** Time course of stimulus-selective adaptation. The blue line shows the mean difference across all units of the responses to S2 in alternation trials and the responses to S2 in repetition trials. Shaded blue bands indicate the 95% bootstrapped confidence interval. The red line shows, for comparison, the normalized net response to S2 in repetition trials (right y axis). Shaded red band indicates the standard error of the mean. **D.** Left, population PSTHs of the normalized net response to the presentation of a stimulus at the foveal position as S1 (blue) or as S2 following the presentation of a white square at 16° in the ipsilateral visual field (red). The response to the presentation of the white square as S1 is shown in black. Right, distribution of ACI, computed for the comparison between the stimulus presented at the foveal position as S1 and as S2 following the white square. Same conventions as in Figure 3.

1075

1076 **Figure 7. Spatial generalization of stimulus-selective adaptation for different distances**
1077 **between adapter and test stimulus.** Median SSACI computed for the full (left column) and
1078 the second (right column) time window (T2, [150,250]; see Results) as a function of the
1079 distance between adapter and test stimuli for the foveal (**A**) and peripheral (**B**) test
1080 positions. Same conventions as in Figure 5.

Figure 8. Stimulus-selective adaptation at peripheral S2 positions. A, B. Each row shows the data for a different adapter-test position combination, as indicated by the panels on the left column. **A.** Population PSTHs of the normalized net response to the presentation of a

1085 stimulus, A or B, presented at a peripheral position as S2 during repetition (red) and
1086 alternation (cyan) trials. **B.** Distributions of SSACI, separated per monkey (M1, green; M2,
1087 yellow). Same conventions as in Figure 3. **C.** Median SSACI computed separately for two time
1088 windows, T1 (left, [50,150]), capturing the peak response, and T2 (right, [150,250]),
1089 capturing the later sustained phase. The circles represent the median values, the vertical
1090 lines the bootstrapped 95% confidence intervals. Each row shows the data for a different S2
1091 position (indicated on the right). For each S2 position, data for the smaller distance between
1092 adapter and test stimulus (Near) are shown in black, for the larger distance (Far) in red. The
1093 red dashed boxes highlight the conditions with the highest distance between adapter and
1094 test stimuli for which stimulus selective adaptation was present (up to 18°).

Figure 9. Stimulus-selective adaptation without excitatory response to the adapter. A.

Median ACI as a function of the normalized net response to the adapter (bin size, 0.1; step size, 0.05) for S2 presented at the foveal position, in repetition (red) and alternation (green) trials. Shaded bands indicate 95% bootstrapped confidence intervals. For each unit, the net responses to the adapter were normalized by the maximum net response across the 8 S1 positions. For the repetition trials, the maximum response was computed for the

1102 presentation of the same image as the test stimulus, whereas for alternation trials it was
 1103 computed across both adapter stimuli (A and B). Medians of the data points with a
 1104 normalized net response < 0.3 have been omitted for the sake of clarity. N denotes the
 1105 number of data points, being the number of units x stimulus (A or B) x adapter position. **B, C,**
 1106 **E, F.** Magenta, population PSTH of the normalized net responses for cases in which the mean
 1107 normalized net response to the adapter was between -0.3 and 0 (**B, C**), and, when, in
 1108 addition, the mean normalized net response computed for the first time window (T1,
 1109 [50,150]) was < 0 (**E, F**). The vertical dashed magenta lines indicate S1 onset and offset, the
 1110 black dashed lines indicate S2 onset and offset. Blue, population PSTH of the normalized net
 1111 response to S1 presented at the fovea, for the same selection of cases. For comparison, the
 1112 response to S1 is shifted along the time axis to align it with the response to S2. Shaded bands
 1113 indicate SEM. N denotes number of cases, as the number of units x positions. **B, E.**
 1114 Repetition trials. **C, F.** Alternation trials. **D, G.** Time course (bin size, 100 ms; step size, 10 ms)
 1115 of the median difference in ACI between repetition and alternation conditions. Dashed
 1116 vertical lines indicate S2 onset and offset, respectively. Shaded bands indicate 95%
 1117 confidence intervals, computed as described in the Results. N denotes the number of cases,
 1118 as the number of units x positions. **D.** Cases with the mean normalized net response to the
 1119 adapter between -0.3 and 0. **G.** Cases with the mean normalized net response between -0.3
 1120 and 0, and, in addition, the mean normalized net response computed for the first time
 1121 window (T1, [50,150]) < 0 .