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The effect of face inversion for neurons inside and outside fMRI-defined face-selective cortical regions

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Taubert J, Van Belle G, Vanduffel W, Rossion B, Vogels R. The effect of face inversion for neurons inside and outside fMRI-defined face-selective cortical regions. *J Neurophysiol* 113: 1644–1655, 2015. First published December 17, 2014; doi:10.1152/jn.00700.2014.—It is widely believed that face processing in the primate brain occurs in a network of category-selective cortical regions. Combined functional MRI (fMRI)-single-cell recording studies in macaques have identified high concentrations of neurons that respond more to faces than objects within face-selective patches. However, cells with a preference for faces over objects are also found scattered throughout inferior temporal (IT) cortex, raising the question whether face-selective cells inside and outside of the face patches differ functionally. Here, we compare the properties of face-selective cells inside and outside of face-selective patches in the IT cortex by means of an image manipulation that reliably disrupts behavior toward face processing: inversion. We recorded IT neurons from two fMRI-defined face-patches (ML and AL) and a region outside of the face patches (herein labeled OUT) during upright and inverted face stimulation. Overall, turning faces upside down reduced the firing rate of face-selective cells. However, there were differences among the recording regions. First, the reduced neuronal response for inverted faces was independent of stimulus position, relative to fixation, in the face-selective patches (ML and AL) only. Additionally, the effect of inversion for face-selective cells in ML, but not those in AL or OUT, was impervious to whether the neurons were initially searched for using upright or inverted stimuli. Collectively, these results show that face-selective cells differ in their functional characteristics depending on their anatomicofunctional location, suggesting that upright faces are preferably coded by face-selective cells inside but not outside of the fMRI-defined face-selective regions of the posterior IT cortex.

electrophysiology; face representations; face-selective cells; inversion effect; IT cortex

HUMANS CAN RECOGNIZE FACES across a variety of viewing conditions. However, turning faces upside down makes them harder to detect, for instance in a visual scene (Andrews and Schluppeck 2004; Garrido et al. 2008; Kanwisher et al. 1998; Lewis and Edmonds 2005; Parkin and Williamson 1987; Purcell and Stewart 1986, 1988; Rossion et al. 2011; Rousselet et al. 2003; VanRullen 2006), and more difficult to discriminate from each other (Diamond and Carey 1986; Yin 1969; see Rossion 2008 for review). These observations indicate that canonical orientation is an important component of face perception and imply that the brain builds cortical representations of faces that are sensitive to changes in picture-plane inversion. Empirical support for this notion has come from functional MRI (fMRI) studies that measured differences in MR signal intensity while human subjects were viewing upright and inverted faces. In general, these studies have shown a reduction of neural activity in face-selective areas (i.e., areas that respond significantly more to faces than objects) of the ventral visual pathway, particularly in the fusiform face area (FFA; e.g., Gilaie-Dotan et al. 2010; Grotheer et al. 2014; Haxby et al. 1999; James et al. 2013; Kanwisher et al. 1998; Mazard et al. 2006; Strother et al. 2011; Yovel and Kanwisher 2005).

There is strong evidence from valid assessments of behavior that numerous nonhuman primate species also have more difficulty detecting (*Pan troglodytes*, Tomonaga 2007; *Macaca fuscata*, Nakata et al. 2014) and discriminating (*P. troglodytes*, Dahl et al. 2013; *Cebus apella*, Pokorny et al. 2009a,b, 2011; *M. nemestrina*, Overman and Doty 1982; *M. fuscata*, Tomonaga 1994; *M. mulatta*, Adachi et al. 2009; Dahl et al. 2007, 2010a,b, 2011; Vermeire and Hamilton 1998) faces after they have been turned upside down. Monkey fMRI studies, on the other hand, have yielded mixed results with respect to which area shows face inversion effects (FIE). Pinsk et al. (2009) reported that the middle face patches [both ML and MF, as defined by Tsao et al. (2006)] together with the anterior lateral face patch (AL) were activated more by upright than inverted faces, whereas the most anterior face patch, AM, was tolerant to inversion. Conversely, another study compared upright and inverted face representations in monkey inferior temporal (IT) cortex using fMRI and claimed that a larger inversion effect was found in the anterior than in the posterior face patches (Bell et al. 2009). However, in these studies, the fMRI responses were averaged across multiple regions of interest and no statistics were made available, making it difficult to draw clear conclusions.

Also, the few single-unit studies that asked whether the orientation of a face changes the firing rate of cells in macaque IT cortex produced inconsistent results across studies. One study reported that inverting faces increased response latencies of face-selective neurons in or close to the fundus of the superior temporal sulcus (STS; Perrett et al. 1985), but there was no consistent difference in firing rate for upright and inverted faces in the small number of cells that were examined (see also Perrett et al. 1982). Tsao et al. (2006) reported that the response of face-selective neurons in the fMRI-defined face-selective patch ML is decreased for inverted compared with upright faces but did not compare this result with other regions of IT cortex. The difference between the two sets of studies may be related to the different locations of the face-selective neurons in the studies. In the present study, we extend these previous studies by investigating whether turning faces upside

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down has an impact on all face-selective cells, irrespective of their location within IT cortex, or whether the inversion effect is present in face-selective cells clustering in (a) category-selective cortical region(s).

We address this question by recording in three regions in monkey IT cortex. Two of these regions are face-selective patches, identified using an fMRI localizer (the middle lateral face patch, ML, and the anterior lateral face patch, AL). In addition to previous studies that targeted face-selective cells in fMRI-defined face patches, we also recorded in the region between ML and AL on the lower bank of STS (a region hereby referred to as OUT). For every neuron we found with a preference for faces over nonface objects, we selected an effective face from an independent stimulus set and then tested the responses of the neurons by presenting the effective face stimulus both upright and inverted. If inversion has a uniform effect on all face-selective cells, then we would expect no differences among our three recording regions. Alternatively, if the face-selective cells clustered in face-selective regions differ functionally from those scattered throughout non-face-selective IT cortex, we would expect a lower inversion effect for the latter populations of cells.

In addition to turning faces upside down, we manipulated the position of the stimuli relative to fixation because electrophysiological evidence has recently emerged indicating that the posterior face patches (PL and, to some extent, ML) are tuned to the eyes of a face when presented in the upper visual field (Issa and DiCarlo 2012). Thus we might also expect lower firing rates when inverted faces are presented foveally simply because inversion effectively moves the eyes away from the upper visual field. Thus the inversion effect may simply reflect an upper field receptive field bias of neurons responding preferably to eye features. In light of this previous work, it was important to ask whether inversion effects in ML, OUT, and AL exist independent of screen position. To do so, we tested single cells with an effective face stimulus (both upright and inverted) in three positions of the screen requiring the monkeys to fixate on different facial features and assessed whether the inversion effect was present at each of these positions.

Turning to the procedure, it was also critical to determine how searching and selecting neurons using upright stimuli contributes to increased firing rates for upright faces over their inverted counterparts. For this reason, we included a dual search procedure whereby "upright search units" were discriminated using upright stimuli (faces and nonface objects) and then the most effective face was selected from a set of upright faces. On the other hand, "inverted search units" were searched for with faces and nonface objects that were inverted and the most effective face was selected from a set of inverted faces. If a mere search bias for upright faces would explain the higher response for upright compared with inverted faces, then one would expect an interaction between face orientation and search procedure whereby the inverted faces would produce a stronger response when searching with inverted stimuli.

METHODS

Subjects and Localization

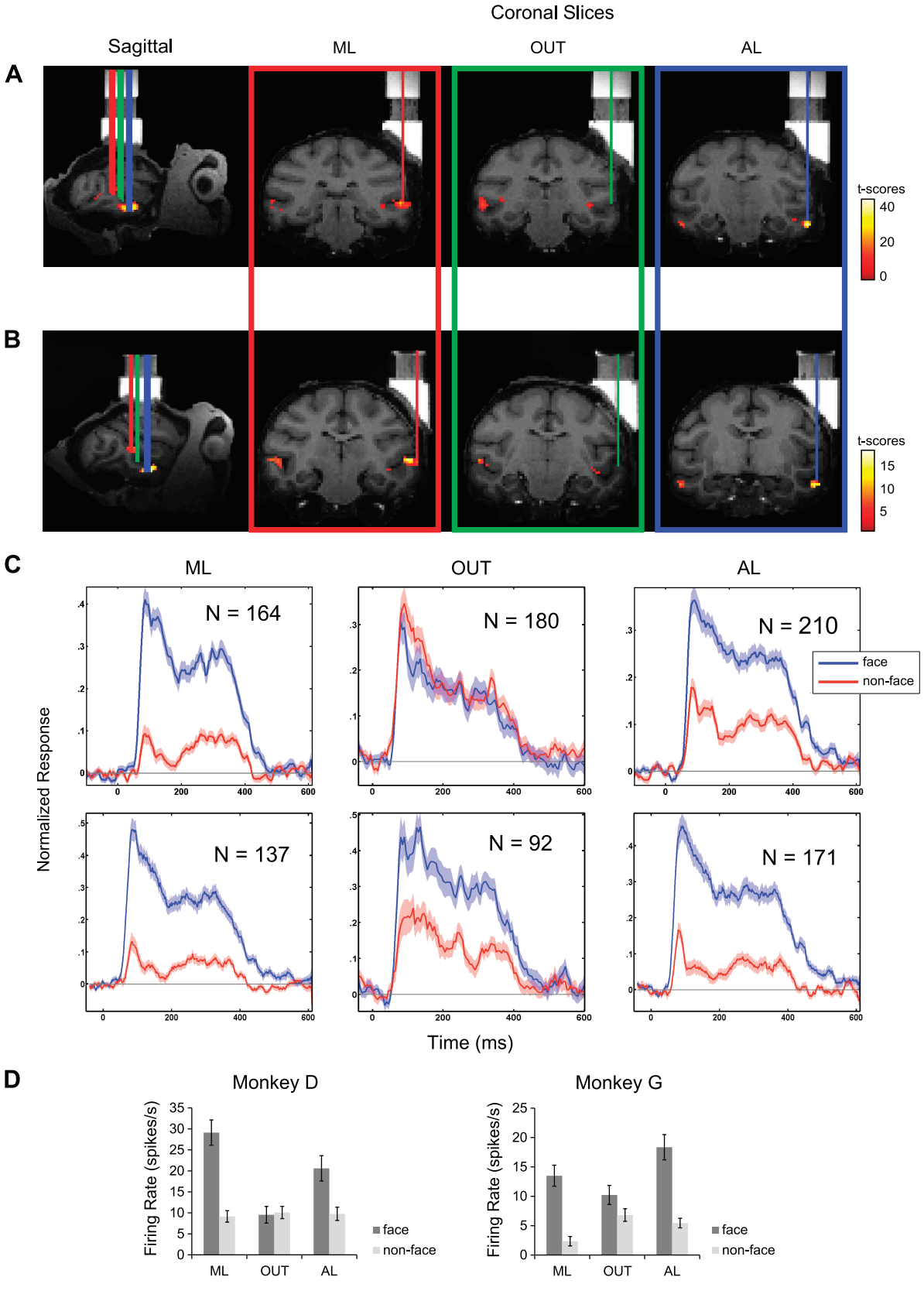
We used fMRI to localize the face-selective patches in two male monkeys (*M. mulatta*), *D* and *G*. Animal care and experimental procedures were approved by the ethical committee of the KU Leuven Medical School. To optimize the signal-to-noise ratio, we used an iron oxide contrast agent [8–11 mg/kg; monocrystalline iron oxide nanoparticle or MION; Feraheme; AMAG Pharmaceuticals, Lexington, MA; more details of this procedure are described elsewhere (Vanduffel et al. 2001)]. Eighty images of faces, bodies, fruits, manmade objects, and hands (16 images per category) were presented to the monkeys in blocks during continuous fixation. These images have been used to isolate face-selective cells in previous studies of rhesus monkeys (Moeller et al. 2008; Tsao et al. 2006) and were presented on a square canvas with a height that subtended a visual angle of 8°. Functional MRI images were acquired using a custom-made 8-channel monkey coil and a gradient-echo single-shot echo-planar imaging sequence [repetition time (TR) = 2 s, echo time (TE) = 17 ms, flip angle = 75°, 80 × 80 matrix, 40 slices, no gap, 1.25-mm isotropic voxel size]. Slices were oriented transversally to cover the whole brain. For more details about data processing, see Popivanov et al. (2012).

Consistent with previous reports, there were several discrete regions (face-selective patches) in both monkeys that responded more to faces than the four other nonface categories. The resulting *t*-maps were thresholded at $P < 0.05$, familywise error, corresponding to a $t > 4.9$ (Fig. 1*A*). Single-unit recordings were performed in three regions in the right hemisphere of both subjects. All recordings were in the lateral lip of the lower bank of the STS (Fig. 1, *A* and *B*): ML, AL, and between these two face patches ("outside of the face patches"; OUT). ML was located ~4 mm anterior to the interaural line in *monkey D* and ~6 mm anterior to the interaural line in *monkey G*. The right lateral anterior face-selective patch (hereby referred to as "AL") was located ~12 and ~13 mm in front of the interaural line in *monkeys D* and *G*, respectively (Fig. 1*A*). OUT was selected as a region that showed no stronger fMRI activation for faces compared with the control stimuli. The selected OUT region was between ML and AL in both monkeys (with a minimum 2-mm distance from either). OUT recording positions were on the lateral edge of the lower bank of STS. This area extended 3 and 2 mm in the anterior-posterior dimension in *monkeys D* and *G*, respectively (Fig. 1*A*).

Single-Cell Procedure and Analysis

Category-search procedure. We surgically implanted a plastic recording chamber in both monkeys that targeted ML and AL and isolated 882 single neurons in total, using Epoxylite-insulated tungsten microelectrodes (in situ measured impedance between 1 and 1.7 MΩ; FHC) and standard electrophysiological procedures described in detail elsewhere (Popivanov et al. 2014; Sawamura et al. 2006). Stimuli were displayed on a CRT display (1,024- × 768-pixel screen resolution, 75-Hz vertical refresh rate; Philips Brilliance 202P4) at a distance of 57 cm from the monkey's eyes. The 32 images (16 faces and 16 nonface objects) that were used to search for responsive neurons and measure their face selectivity were taken from the 80 that were used in the fMRI block-design localizer. The 16 nonface objects were taken from 4 different categories (headless bodies, hands, gadgets, and fruits), selected to be similar to faces in their round shape (e.g., an orange or a closed fist). All images were 8° of visual angle in height, and width was allowed to vary. For electrophysiological recordings, however, the noise background was removed from these images and replaced with a uniform gray background and then gamma-corrected. These images were presented in their canonical orientation for the upright search units and were rotated 180° for the equivalent inverted search units [see Fig. 2*A* for procedure and Tsao et al. (2003) for stimuli]. We searched for upright and inverted units within each recording session, alternating between the two search procedures. The position of one eye was continuously tracked by means of an infrared video-based tracking system (sampling rate 1 kHz; SR Research EyeLink).

A monkey initiated a trial by fixating on a central fixation spot (size = 0.2° of visual angle) that was always present throughout the trial. The


Coronal Slices
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N = 210
face
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N = 137
N = 92
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Normalized Response
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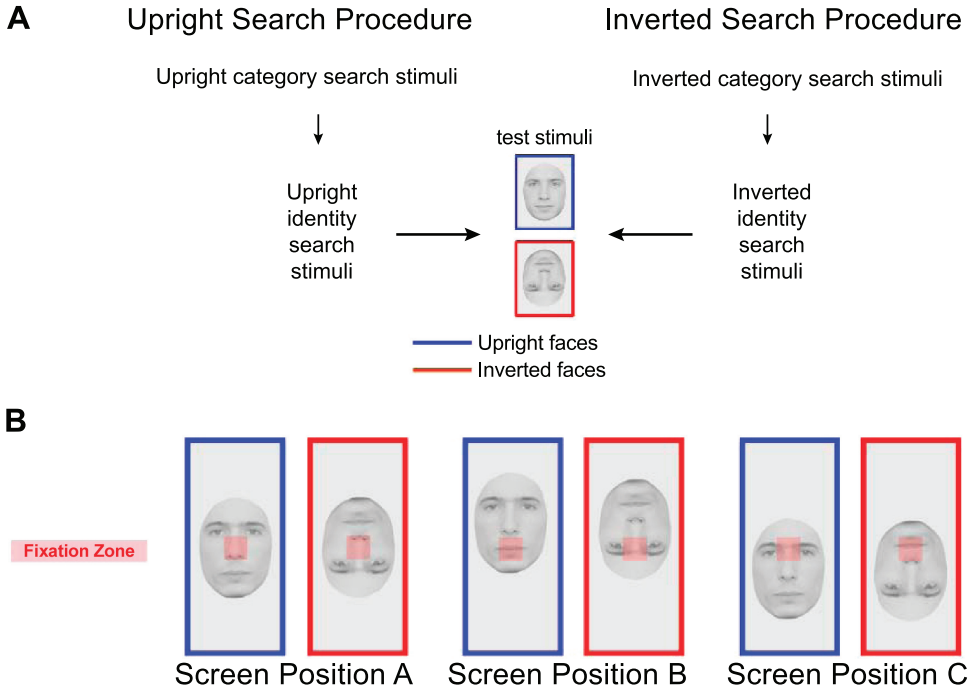


Fig. 2. Procedure and stimuli. *A*: schematic representing the experimental procedure used to test "upright search units" (left) and "inverted search units" (right). Note all inverted experimental stimuli were created by rotating each stimuli 180° in the picture plane. This figure only provides a flow chart for the procedure; in most cases, the stimuli have been darkened. *B*: illustrative examples of stimuli used in the position tolerance test with the fixation zone overlaid on the stimuli to indicate the features the monkey was asked to fixate on.

monkey was then required to fixate on this spot (within a 2 × 2° fixation window) for 300 ms before stimulus onset and during the stimulus presentation (300 ms). An additional 300-ms fixation period after stimulus offset was required before the monkey was rewarded for continuous fixation with a fluid reward. Trials were separated by an interstimulus interval of at least 500 ms, although the exact duration was dependent on the oculomotor behavior of the monkey as fixation was required to initiate each trial. In the main tests, the stimuli were at the center of the screen, behind the fixation spot. Each trial presented a monkey with a single stimulus, drawn from the set in a pseudorandom order. Each stimulus was repeated at least twice for every neuron discriminated. In each recording session, we recorded the first single unit encountered at the predetermined depth with respect to the silence associated with the sulcus, regardless of face selectivity or visual responsiveness. Each unit thereafter was at least 150 μm deeper than the previous one.

Offline, the firing rate of a unit was computed for every trial in two analysis windows: Baseline (−250 to 50 ms relative to stimulus onset) and Response (50–350 ms). Responsiveness to the stimuli was tested using a split-plot ANOVA with as repeated factor, Window (Baseline vs. Response), and as between-trial factor, Stimulus. Only units for which there was a significant main effect of Window or a significant interaction between Window and Stimulus were included in further analyses. All subsequent analyses were performed on baseline subtracted (net) responses. Following previous studies (Freiwald and Tsao 2010; Tsao et al. 2006), we defined for each responsive unit a face selectivity index as FSI = (mean net response$_{\text{faces}}$ − mean net response$_{\text{nonface objects}}$)/(|mean net response$_{\text{faces}}$| + |mean net response$_{\text{nonface objects}}$|). The same analysis windows as those for the ANOVA (see above) were employed. A unit was only considered to be a face cell when FSI > 0. This criterion was set because we were recording an area (OUT) that was not activated by faces at a population level, unlike ML and AL, and thus we needed to restrict analyses to neurons that responded more to faces than nonface objects. Note that Bell et al. (2011) employed the same conservative definition of face selectivity. To pool across neurons and monkeys, we normalized the data with respect to the maximum response across stimuli for each neuron using the same analysis window.

Effective face search procedure. Every neuron that responded to faces of the category-search procedure was tested with a set of 24 achromatic faces of unfamiliar adult Caucasian individuals (12 male) with a neutral expression (see Fig. 2*A* for an example stimulus; all faces available from http://face-categorization-lab.webnode.com/resources/). The height of these stimuli subtended 10° of visual angle, but the timing parameters were identical to those described for the category-search procedure. All images depicted neutral expressions and the front most viewpoint. External cues to facial identity (e.g., hair, ears, and neck) were removed using Adobe Photoshop. The luminance and root-mean-square (RMS) contrast of all stimuli were adjusted to match the mean luminance and contrast values of the

Fig. 1. Recording locations and face category selectivity. *A*: recording regions in *monkey D*. On the far left is a sagittal section through the right hemisphere of *monkey D* showing face-selective activation (ML and AL) along the lip of superior temporal sulcus (STS) that were obtained using the functional MRI (fMRI) localizer. Single-unit recordings were targeted to 3 regions; the most posterior recordings (indicated with a red line) targeted ML, the most anterior recordings (indicated with a blue line) targeted AL, and finally the OUT recordings were taken from the region in between ML and AL where there was no significant fMRI activation (indicated with a green line). To the right of the sagittal are 3 coronal slices, rotated into the coordinate system of the recording grid, showing the center of ML, OUT, and AL. Monocrystalline iron oxide nanoparticle (MION) activation is superimposed on a high-resolution anatomic scan obtained with tungsten markers positioned in the recording chamber grid. *B*: recording regions in *monkey G*. These are presented in the same way as for *monkey D* above. *C*, *top* row: average normalized net responses for all responsive units to faces and nonface objects presented in smoothed peristimulus time histograms (bin width 20 ms, step size 5 ms). Before averaging across neurons, the firing rate of each neuron was normalized with respect to its peak firing rate (determined with the same bin) for the face and nonface conditions. There are separate histograms for each region (from left to right, ML, OUT, and AL). Stimulus onset corresponds to 0 ms. Transparent bands indicate the standard error of the mean. *Bottom* row: average normalized net responses for neurons with a face selectivity index (FSI) >0 presented in smoothed peristimulus time histograms (same conventions as *top* row). *D*: average net response of neurons recorded in *monkey D* (*left*) and in *monkey G* (*right*). Error bars represent standard error of the mean. The responses to the different stimuli of each category were averaged. Because many neurons showed selectivity within each category, the averages underestimate the maximum response strength to individual images (see Fig. 3*C* for response strengths to more effective stimuli).

entire image set. When a given unit had been selected using the upright search procedure, these faces were presented upright (Fig. 2*A*), whereas when a unit had been selected using the inverted search procedure, these faces were presented upside down. The faces were presented interleaved in a pseudorandom order for at least 2 presentations per face (average number of presentations per face: 3). Based on visual inspection of the online peristimulus time histograms for the 24 faces, we selected the face stimulus that produced the largest response for further testing.

Orientation test. We examined whether a unit responded differentially to an effective face stimulus depending on picture-plane orientation. The 2 conditions analyzed here were part of a design including 10 conditions in total. These conditions were the same regardless of whether the unit was selected using the upright or inverted search procedure (Fig. 2*A*). The order of these conditions was in such a way that each condition was presented an equal number of times in a pseudorandomized interleaved fashion. On average, we collected 11 unaborted trials per condition (a minimum of 6). Units that did not respond significantly to at least 1 of the 2 conditions of interest (upright or inverted), determined by a split-plot ANOVA in the same way as described for the category-search procedure, were excluded from the sample at this point. The other 8 conditions presented the subjects with face stimuli that had been phase-scrambled or had content diminished with various spatial frequency filters (these fall outside of the scope of this paper). We analyzed average net firing rate, without normalization, because only 2 conditions were being included in the analysis.

Position tolerance test. In the above orientation test, the eyes of each stimulus were presented in the upper visual field in the upright condition and in the lower visual field in the corresponding inverted condition. Issa and DiCarlo (2012) reported that neurons in the posterior face-patch PL and also ML respond to features in the upper visual field. If neurons in our recording regions respond more strongly to the high-contrast eye region than the mouth, an inversion effect in the orientation test could be attributed to a systematic shift in location of the eye region. To rule out this explanation, we, therefore, presented the upright and inverted faces at three vertical locations in a subsequent position tolerance test (Fig. 2*B*).

We ran the position tolerance test using an effective identity and the same timing parameters as described for the orientation test. In the position tolerance test, there were two levels of Face Orientation (upright vs. inverted), which were repeated for each level of Screen Position (hereby denoted as *Screen Positions A*, *B*, and *C*). For *Screen Position A* trials, the stimuli were presented at the center of the screen, as in the previous tests. As a consequence, the monkeys were fixating on the nose region, and the eyes were being displayed above or below the acceptable fixation zone depending on the orientation of the face (Fig. 2*B*). Faces presented in *Screen Position B* were shifted upward, relative to the central fixation point, so that the monkeys would fixate on the mouth in the upright condition and the eyes in the inverted condition. Conversely, faces were shifted downward in *Screen Position C* in such a way that the monkeys were fixating on the eyes of the upright face and the mouth of the inverted face. For each of the six unique conditions, presented interleaved in a pseudorandom manner, we collected at least eight unaborted trials. Unlike the orientation test, there were more than two conditions in the position tolerance test, so the average net firing rate of each neuron was normalized to its maximum response across all six unique conditions to ensure the statistical outcomes were not driven by the neurons with the highest firing rates.

We first analyzed a sample that included all responsive units determined by a split-plot ANOVA with Window (Baseline and Response) and Condition (upright / *Screen Position A*; inverted / *Screen Position A*, upright / *Screen Position B*, inverted / *Screen Position B*, upright / *Screen Position C*, inverted / *Screen Position C*) included as factors. Second, we analyzed a restricted sample that consisted of face-selective cells only (units with an FSI >0). The position tolerance test was designed to test whether inversion effects were preserved across changes in screen positions, and thus we compared the average response of the single units with each of the conditions in a repeated-measures factorial ANOVA. The reported statistics have been adjusted for potential violations of sphericity using the Greenhouse-Geisser correction.

In a final analysis, we selected at random 15 units from each region that responded more strongly to the upright face than the inverted face when stimuli were presented in the central screen position (*Screen Position A*). For these neurons that showed an inversion effect, we then tested whether the effect was preserved at the other locations. To do this, we excluded *Screen Position A* data and, for each recording region, ran a 2×2 repeated-measures ANOVA with Screen Position (*B* vs. *C*) and Face Orientation (upright vs. inverted) included in the design.

RESULTS

Face Category Selectivity

The face-selective regions, ML and AL, were localized using standard monkey fMRI procedures (Vanduffel et al. 2001) in two male monkeys that were trained to fixate on a small central fixation point while images of achromatic faces and objects were presented at the center of the screen.

Using the category-search procedure, we confirmed that the average firing rate was greater for faces than for nonface objects for responsive units in the two face regions, which was not true for the population of responsive units isolated in the OUT region (Fig. 1*C*). The average FSI of all of the recorded neurons was markedly higher in ML and AL than it was outside of the face patches (ML, average FSI = 0.61, $n = 164$; AL, average FSI = 0.40, $n = 210$; OUT, average FSI = -0.08, $n = 180$; Kruskal-Wallis ANOVA, $P < 0.001$; Fig. 1*C*). Despite the difference in stimuli, the average FSIs in the face-selective patches are in the same range as those reported by Issa and DiCarlo (2012) but lower than that of Tsao et al. (2006) for ML. The lower FSI compared with that of Tsao et al. (2006) may be because our control stimuli included a higher proportion of rounded objects and ML neurons are known to show some responses to such shapes. Also, we used a smaller set of stimuli than Tsao and colleagues (2006) that might have led to a lower estimate of population face selectivity. Another consideration is that the neurons in ML are more viewpoint-selective than those in other regions of the cortical face processing system defined in fMRI, and the majority of our stimuli were frontward facing. Importantly, the OUT neurons showed no face selectivity on average, in agreement with the fMRI mapping [consistent with the findings of Bell et al. (2011)]. When the samples were limited to neurons with an FSI >0, the average face selectivity in area OUT, however, became more comparable with areas ML and AL (Fig. 1*C*; ML, average FSI = 0.67, $n = 137$; AL, average FSI = 0.58, $n = 171$; OUT, average FSI = 0.45, $n = 92$; Kruskal-Wallis ANOVA, $P < 0.001$). Individual monkey data are provided in Fig. 1*D*.

Face-Selective Cells Respond More to Upright Faces than Inverted Faces

We first analyzed all neurons that responded significantly to at least the upright or inverted orientation test condition, irrespective of their FSI measured during the category-search

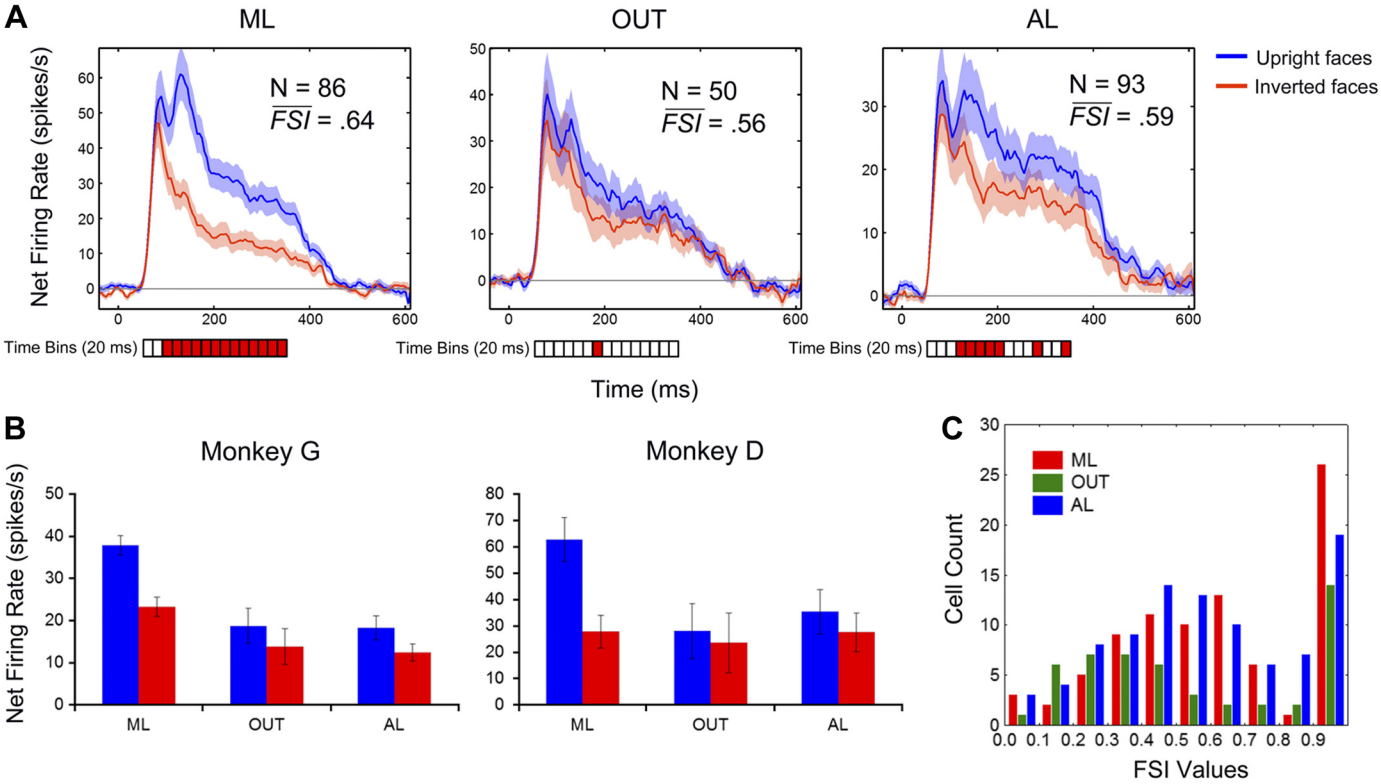


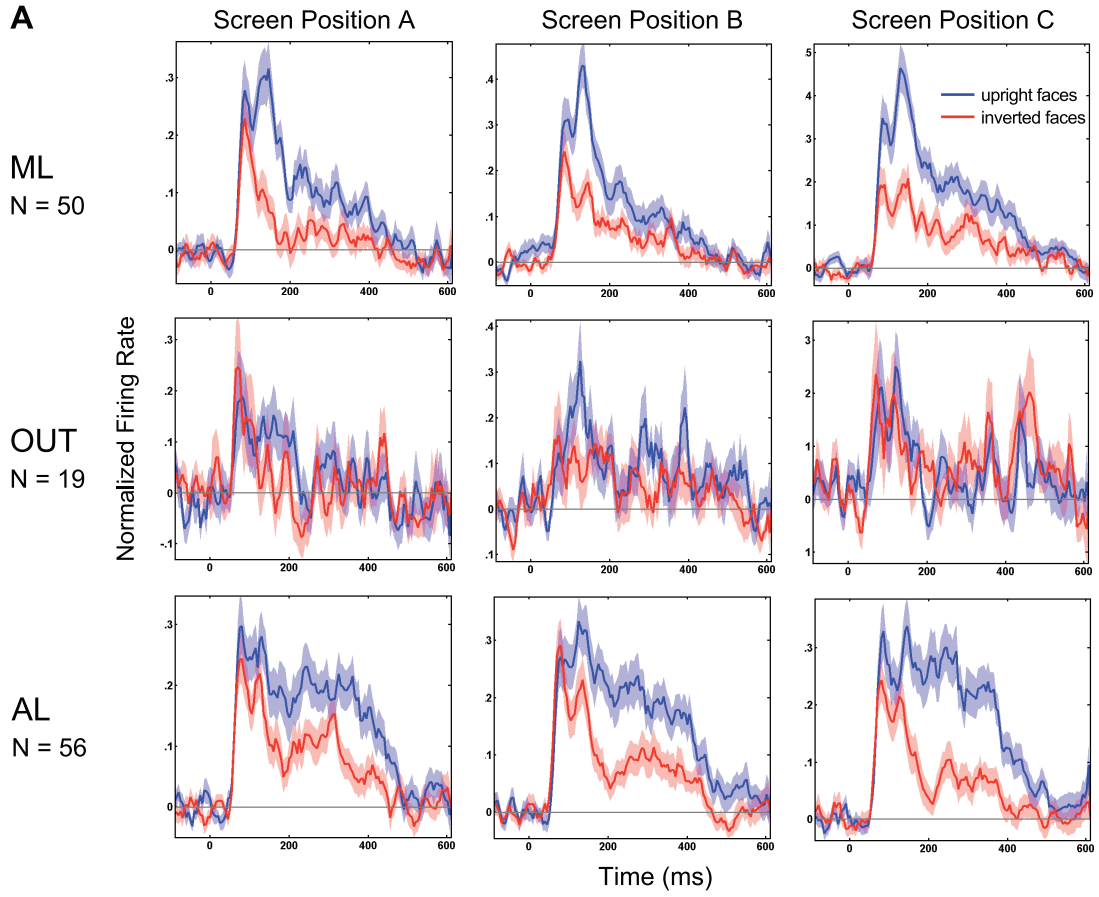
Fig. 3. Orientation test. *A*: smoothed peristimulus time histograms displaying the average net response of all neurons in ML (*left*), OUT (*middle*), and AL (*right*; all with same conventions as Fig. 1*C*) with an FSI >0. Before averaging across neurons, the firing rate of each neuron was normalized with respect to its peak firing rate (determined with the same bin) for the upright face and inverted face conditions. Mean FSI values and sample sizes are indicated. Underneath each histogram is a bar representing the time analysis of the orientation test data. A red box indicates a time bin with a significant difference between orientation conditions. *B*: average net response of neurons recorded in *monkey D* (*right*) and in *monkey G* (*left*). Error bars represent standard error of the mean. *C*: distribution of FSI values for neurons analyzed in each region.

procedure (the sample sizes were 110, 85, and 124 for recording regions ML, OUT, and AL, respectively; Fig. 3*A*). We used a 2 × 3 mixed-design ANOVA with Face Orientation as a repeated factor (upright vs. inverted) and Region (ML vs. AL vs. OUT) as a between-neuron factor. The results revealed that inverting faces decreased the average net firing rate, averaging across recording region [$F(1, 316) = 55.05$, $P < 0.001$], yet there was no evidence of an effect of recording region [$F(2, 316) = 2.37$, $P = 0.09$]. There was also an interaction between the factors [$F(2, 316) = 13.78$, $P < 0.001$] with ML showing the largest inversion effect. We tested the difference between the upright and inverted conditions for each recording region using a series of discrete Wilcoxon signed-rank tests (ML, $P < 0.001$; OUT, $P = 0.005$; AL, $P = < 0.002$; all significant using Bonferroni rule).

Because of the differences in overall face selectivity between our recording regions, however, we limited the next analysis to the subset of neurons that responded more to faces than objects (i.e., FSI > 0; Fig. 3*B*). We recorded 86 thus defined face-selective cells in ML, 50 face-selective cells in OUT, and 93 in AL. The FIE was confirmed by a main effect of Face Orientation [$F(1, 226) = 41.51$, $P < 0.001$]. Again, there was no main effect of Region [$F(2, 226) = 1.55$, $P = 0.214$], and the interaction between these effects was significant [$F(2, 226) = 7.09$, $P < 0.001$]. All pairwise comparisons (Wilcoxon signed-rank tests) were significant after Bonferroni correction (ML, $P < 0.001$; OUT, $P = 0.003$; AL, $P < 0.001$; Fig. 3*A*).

On these data, an additional analysis was run to determine when, in time course, the inversion effects emerged in each recording region. To do this, the original response window (300 ms, staring from 50 ms after stimulus onset) was subdivided into 15 bins, each 20 ms in length. The differences between the upright and inverted conditions were tested in each bin using a Wilcoxon signed-rank test. All 15 tests were corrected using false discovery rate (FDR; q-values < 0.05; Fig. 3*B*). In area ML, all contrasts were significant from 90 ms (after stimulus onset) onward. In area OUT, the inversion effect was only significant in 1 time bin (170–190 ms after stimulus onset). In area AL, there were 3 time points after stimulus onset where we found a significant inversion effect (from 110 to 210, 250 to 270, and 330 to 350 ms). Individual monkey data are available in Fig. 3*B*.

To quantify the magnitude of the FIE for each single neuron, we calculated an orientation index [OI = (mean response upright face − mean response inverted face)/(mean response upright face + mean response inverted face)]. Pooling data from across all three recording regions, the average OI for face-selective cells (FSI > 0) was 0.15 (SD = 0.30, range = −0.87 to 1), with mean OIs (SD) for ML, AL, and OUT being 0.20 (0.31), 0.11 (0.28), and 0.12 (0.32), respectively. Wilcoxon tests (1-sample) revealed a significant FIE in each of the three patches (ML, $P < 0.001$; AL, $P < 0.001$; OUT, $P = 0.003$). When we examined the relationship between FSI and OI for the neurons with an FSI >0, we found no indication that the degree of face selectivity predicted the impact of face



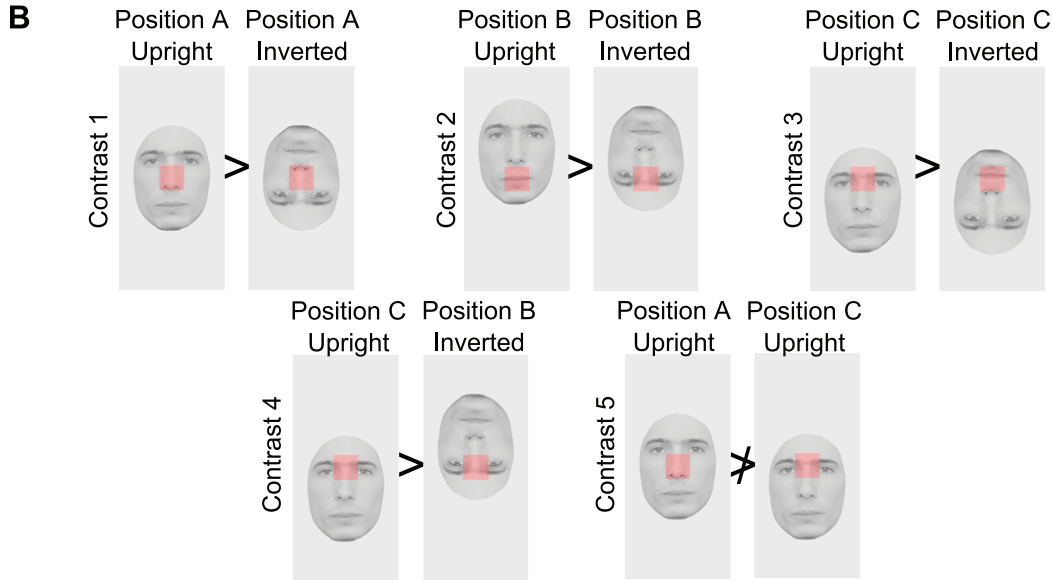


Fig. 4. Examination of position tolerance of the face inversion effect. *A*: smoothed peristimulus time histograms illustrating the average normalized response for face-selective cells (FSI > 0) in each region (*top*, ML; *middle*, OUT; and *bottom*, AL) to upright faces and inverted faces per screen position (*Position A* on the *left*, *Position B* in the *middle*, and *Position C* on the *right*). Errors bars represent standard error of the mean. *B*: schematic of the screen position tolerance stimuli indicating the 5 contrasts of interest. Symbols represent the expected direction of the differences. *Contrasts 1–3* simply tested for the presence of the inversion effect at each *Screen Position* (*A–C*). *Contrast 4* compared "*Position C* Upright" with "*Position B* Inverted" because in both conditions the monkey was fixating on the same feature (the eyes) but the face was rotated 180°. We expected that this should induce an inversion effect. *Contrast 5* compared "*Position A* Upright" with "*Position C* Upright" because in both conditions the face remained upright but the eyes were shifted from the upper to the lower visual field. We expected to see no effect (i.e., response magnitude in *Position A* Upright should not have been greater than in *Position C* Upright).

Table 1. *Position tolerance contrast results*

	ML		OUT		AL	
Contrast	Direction	*P*	Direction	*P*	Direction	*P*
1. Position A upright vs. *Position A* inverted	Upright > inverted	0.0001*	Upright > inverted	0.046	Upright > inverted	0.009*
2. Position B upright vs. *Position B* inverted	Upright > inverted	0.0006*	Upright > inverted	0.797	Upright > inverted	0.004*
3. Position C upright vs. *Position C* inverted	Upright > inverted	0.0001*	Inverted > upright	0.775	Upright > inverted	0.0001*
4. Position C upright vs. *Position B* inverted	*Position C > Position B*	0.0001*	*Position C > Position B*	0.749	*Position C > Position B*	0.003*
5. Position A upright vs. *Position C* upright	*Position C > Position A*	0.001*	*Position C > Position A*	0.689	*Position C > Position A*	0.058

*Significant comparisons.

inversion on the response of a unit, pooling across all face-selective cells recorded in the three regions ($r = -0.05$, $P > 0.05$; $n = 229$).

Screen Position Tolerance

To assess the effect of stimulus location and face inversion on the responses of a neuron in each of the three regions, we ran independent repeated-measures ANOVAs for each region (ML, AL, and OUT) with two factors: Face Orientation (upright vs. inverted) and Screen Position (*A* vs. *B* vs. *C*; Fig. 2*B*).

We first ran the analysis on the responsive units, irrespective of the FSI of a cell (Fig. 4*A*). In area ML ($n = 52$), both main effects were significant [Face Orientation, $F(1, 51) = 44.96$, $P < 0.001$; Screen Position, $F(1.94, 98.78) = 8.85$, $P = 0.001$], but, importantly, there was no evidence of an interaction [$F(1.77, 90.14) = 1.46$, $P = 0.238$]. In area OUT ($n = 24$), there were no significant effects [Face Orientation, $F(1, 23) = 1.31$, $P = 0.264$; Screen Position, $F(1.98, 45.65) = 2.89$, $P = 0.067$; Interaction, $F(1.94, 44.53) = 2.04$; $P = 0.143$]. For neurons in area AL ($n = 59$), there was an effect of Face Orientation consistent with an FIE [$F(1, 58) = 21.66$, $P < 0.001$] but no effect of Screen Position [$F(1.85, 108.18) = 1.51$, $P = 0.227$]. The interaction was also not significant [$F(1.86, 108.02) = 1.28$, $P = 0.281$]. For verification purposes, the same analysis was performed on net data (without normalization) giving the same outcome [ML, Screen Position, $F(1.4, 71.79) = 9.53$, $P < 0.001$, Face Orientation, $F(1, 51) = 38.6$, $P < 0.001$, Interaction, $F(1.44, 73.54) = 0.72$, $P = 0.1$; OUT, Screen Position, $F(1.99, 45.97) = 2.15$, $P = 0.13$, Face Orientation, $F(1, 23) = 0.92$, $P = 0.35$, Interaction, $F(1.80, 41.46) = 0.38$, $P = 0.66$; AL, Screen Position, $F(1.60, 92.91) = 1.72$, $P = 0.18$, Face Orientation, $F(1, 58) = 10.57$, $P = 0.002$, Interaction, $F(1.73, 100.57) = 0.99$, $P = 0.36$].

We restricted the subsequent analysis to neurons with an FSI >0 (Fig. 4*A*). This criterion lowered the sample size from 52 to 50 in area ML, from 24 to 19 in OUT, and from 59 to 56 in area AL. Averaging across screen positions, face-selective cells in ML responded more to an upright face than its inverted counterpart [Face Orientation, $F(1, 49) = 46.37$, $P < 0.001$]. There was also a main effect of Screen Position [$F(1.9, 93.19) = 14.55$, $P < 0.001$]. Importantly, there was no significant interaction between these factors indicating that the FIE was robust to changes in the screen position [$F(1.69, 82.92) = 0.76$, $P = 0.45$; Fig. 4*A*]. For AL neurons, there was only a main effect of Face Orientation [$F(1, 55) = 28.30$, $P < 0.001$], which, paired with the absence of an interaction between Face Orientation and Screen Position [$F(1.97, 108.26) = 2.12$, $P = 0.13$], implies that the FIE in AL was also robust to screen position (Fig. 4*A*). There were no significant effects among face-selective cells found outside of the face patches [Face Orientation, $F(1, 18) = 1.28$, $P = 0.27$; Screen Position, $F(1.96, 35.23) = 2.42$, $P = 0.10$; Interaction, $F(1.88, 33.79) = 1.30$, $P = 0.28$; Fig. 4*A*]. For each region, five pairwise comparisons (Wilcoxon signed-rank tests, Bonferroni corrected) were run to assess whether there were significant inversion effects at each screen position (*contrasts 1–3*; Fig. 4*B*), to test whether inversion when fixating on the same feature was sufficient for a significant effect (*contrast 4*; Fig. 4*B*), and to verify that moving the stimuli, relative to fixation, was not sufficient for a significant effect (*contrast 5*; Fig. 4*B*). Results for each region (ML, OUT, and AL) are presented in Table 1.

The absence of a position-invariant FIE in this population of face-selective OUT neurons did not result from a position-intolerant stimulus preference of the individual OUT neurons. Indeed, determining the preferred orientation condition (upright or inverted) of each unit at the central screen position and applying this ranking to other screen positions revealed evidence of a preserved stimulus preference in the OUT region (data not shown), as expected from previous studies of single-cell responses in IT cortex (DiCarlo et al. 2012; Li et al. 2009; Vogels and Orban 1996). It is likely that the inversion effect in this smaller sample of OUT face-selective neurons was too variable to exhibit position tolerance at the level of the averaged response. To overcome this, we restricted the final analysis to 15 neurons that responded more to the upright face compared with its inverted equivalent in the standard, central screen position (*Screen Position A*). We equated also the number of such neurons by randomly sampling these neurons from the larger sample of neurons in each of the 3 regions, thus controlling for statistical power in detecting position tolerance of the FIE in the 3 regions. For each recording region, we ran a 2 × 2 ANOVA with Screen Position (*B* vs. *C*) and Face Orientation (upright vs. inverted) included as repeat factors. This analysis yielded the same significant effects of orientation in areas ML [Screen Position, $F(1, 14) = 0.20$, $P = 0.66$; Face Orientation, $F(1, 14) = 28.19$, $P < 0.001$; Interaction, $F(1, 14) = 0.09$, $P = 0.77$] and AL [Screen Position, $F(1, 14) = 0.33$, $P = 0.58$; Face Orientation, $F(1, 14) = 94.04$, $P < 0.001$; Interaction, $F(1, 14) = 1.48$, $P = 0.24$] with no evidence that

this was influenced by screen position. However, despite the same sample size, there was no evidence of any effect among OUT neurons [Screen Position, $F(1, 14) = 0.97$, $P = 0.34$; Face Orientation, $F(1, 14) = 1.74$, $P = 0.68$; Interaction, $F(1, 14) = 0.08$, $P = 0.78$]. Further restricting the sample to the neurons with a statistically significant FIE at *Screen Position A* yielded effects in the 3 regions that were similar to those in the larger samples.

These data beg the question of what is causing the apparent FIE for centrally positioned faces for the face-responsive/-selective neurons (Fig. 3, *A* and *B*) outside of the face patch? Because neurons were searched for using upright faces, a simple explanation of the putative FIE found for neurons outside of the face patches is a search bias. This possibility was examined in the next test.

Face-Selective Cells Outside of the fMRI-Defined Network are Subject to a Search Bias

To assess whether the search and selection procedure of neurons tested in the orientation test biased the responses toward upright faces, we collected an independent sample of neurons using the same search and selection procedure except that all search stimuli (faces and objects) were presented upside down. We recorded 123 inverted search units in ML, with an average inverted-face selectivity index of 0.16. In AL, the average inverted-face selectivity index was 0.12 ($n = 63$). Thus face selectivity was markedly reduced for inverted faces in both face patches. The 113 inverted search units recorded outside of the face patches had an average inverted-face selectivity index of -0.01.

When we applied the criterion for face selectivity (FSI > 0), 42 inverted search units remained in the ML sample, 27 in AL, and 33 in OUT. Searching with an inverted face had a marked impact on the FIE in OUT (Fig. 5): the average OI [-0.20 (SD $= 0.30$)] was significantly below 0, indicating a stronger response to inverted faces compared with upright faces (1-sample Wilcoxon signed-rank test, $P < 0.001$). The results of the orientation test that followed the inverted search test differed between the 2 face patches with a significant FIE [mean OI $= 0.14$ (SD $= 0.29$)] for ML (1-sample Wilcoxon signed-rank test, $P = 0.002$) and no significant inversion effect [mean OI $= -0.05$ (SD $= 0.27$)] for AL (1-sample Wilcoxon signed-rank test, $P = 0.35$).

To assess whether these differences in inversion effects for the 2 search procedures depended significantly on the region, the OIs of the face-selective cells searched with inverted stimuli were combined with those of the face-selective cells identified using the upright search procedure in a 2×3 between-neurons analysis of covariance. In this analysis, both Search Procedure (upright vs. inverted) and Region (ML vs. AL vs. OUT) were included in the model as between-neurons factors, and FSI was the covariate. The latter was done to control for an effect of FSI on the OI. Interactions between FSI and categorical variables were included in the model to verify the homogeneity of slopes [FSI $\times$ Search Procedure, $F(1, 319) = 0.16$, $P = 0.70$; FSI $\times$ Region $F(2, 319) = 0.55$, $P = 0.58$]. Averaged across the recording regions, OI values were higher for upright search units than inverted search units [$F(1, 319) = 5.61$, $P = 0.02$]. There was also a main effect of Region [$F(2, 319) = 6.07$, $P < 0.01$]. Importantly, a significant interaction between Search Procedure and Region [$F(2, 319) = 3.24$, $P = 0.04$] confirmed that the effect of comparing upright and inverted search procedures on the OI was significantly contingent on the recording region.

We performed identical analyses using more stringent criteria for face selectivity: *1*) only neurons that had an FSI >0.333; *2*) only neurons that responded more significantly to faces than nonface objects (Mann-Whitney *U* test, $P < 0.05$); and *3*) neurons with a significantly higher responses to faces than to nonfaces and that had a maximum response to 1 of the 16 faces that was greater than the maximum response to 1 of the 16 nonface stimuli. Despite smaller sample sizes, these analyses yielded the same overall outcome as reported above.

DISCUSSION

Using a very simple image manipulation, 1 with a well-established deleterious effect on primate behavior, picture-plane inversion (Parr 2011; Rossion 2008), we were able to uncover differences in the average response patterns of face-selective cells in and outside of the face-selective regions. Previous macaque single-unit studies did not consistently show an FIE. Perrett and colleagues (1985) reported a tendency for a shorter latency for upright compared with inverted faces, but there was no inversion effect for the response strength of a small sample of face-selective cells. These neurons were possibly recorded in or close to the fundus/upper bank face patch of the mid-STS (MF), and neurons in and outside of the face-selective region were probably mixed. Tsao et al. (2006), recording from ML, found stronger responses for upright compared with inverted faces. However, in these studies, face-selective cells were defined with upright faces, and thus the reported FIE may have reflected a selection bias. In the present study, we explicitly tested for this bias by searching neurons with upright or inverted stimuli. We found that only the FIE in ML, which was found in the early portion of the response of the cells and remained significant for the entire stimulus presentation duration, was robust to the differences in search strategy.

A second critical factor to consider when examining a putative FIE is its tolerance to changes in vertical image location. Inverting a face changes the spatial location of facial features, and this in combination with a bias in the receptive field location (Issa and DiCarlo 2012) may produce an FIE. By explicitly testing the effect of a vertical spatial shift of the face, we could reject this (trivial) explanation of an FIE for the face-patch neurons. Based on the combination of these tests, we can conclude that ML neurons show indeed overall stronger responses to upright compared with inverted faces. These data indicate that, on average, face-selective cells in ML prefer the upright configuration of a face. However, face neurons outside of the face-selective regions at these anterior-posterior levels in IT do not show a consistent FIE since any advantage for upright faces appears transiently in the middle of the stimulus presentation and disappears when controlling for search biases and facial feature location.

Face-selective cells were harder to find when presenting inverted faces compared with upright faces in AL, as it was in ML. This aligns with a previous monkey fMRI study that found FIE in both ML and AL (Pinsk et al. 2009). On the other hand, the FIE measured in AL was abolished (although not

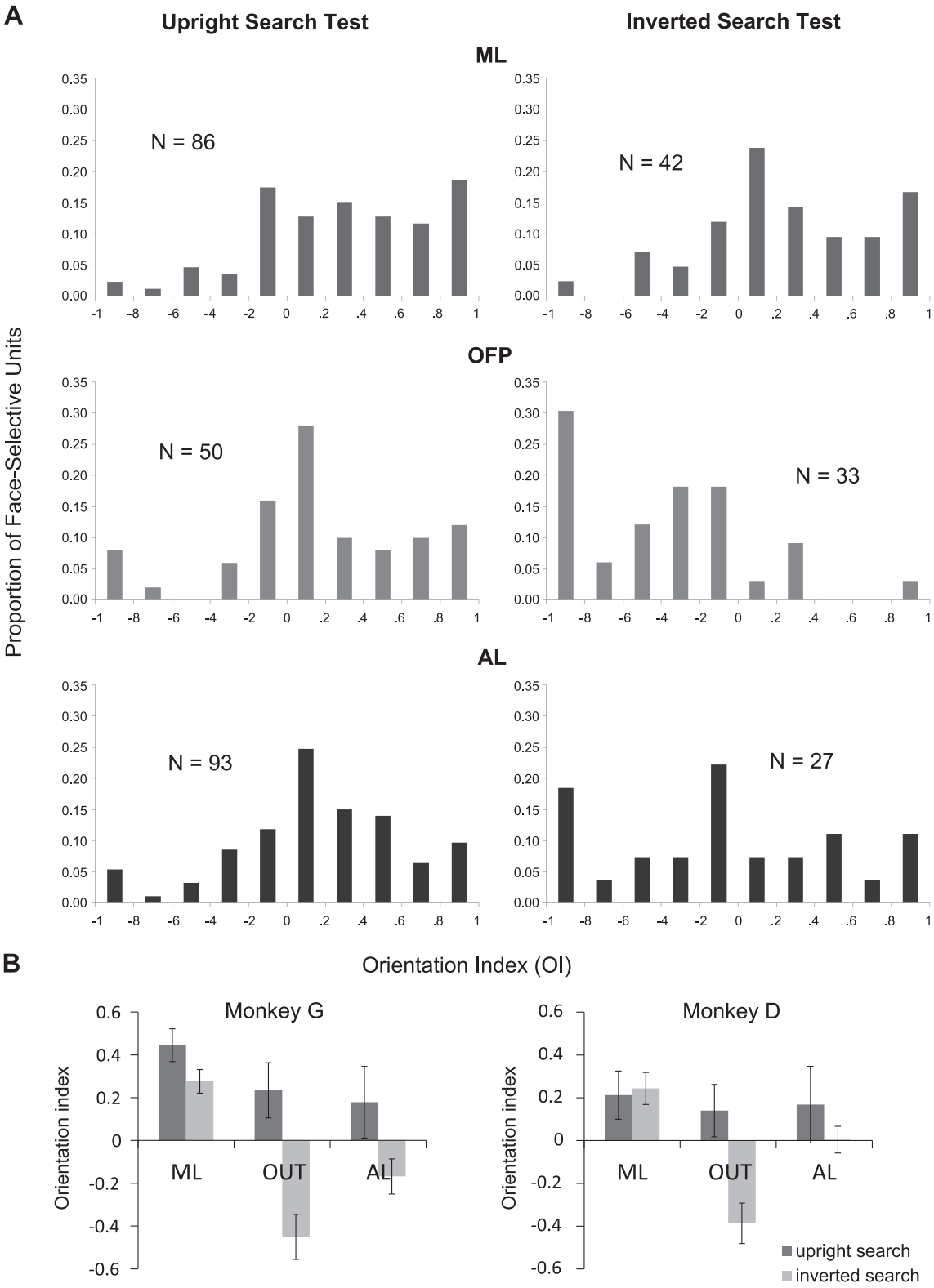


Fig. 5. Distribution of orientation index (OI) values for each recording region and each search procedure. OFP, outside of the face patches.

significantly reversed) when searching with inverted stimuli. At first glance, it is difficult to account for the apparent conflict between the observed search procedure dependency with regard to the FIE and the lower incidence of face units when searching with inverted stimuli in AL. A possible explanation is the potential contribution of external facial features (e.g., hair) to processing in AL. A previous study of face neurons showed the importance of external facial features for face selectivity in ML and MF (Ohayon et al. 2012). A notable difference between the stimuli used in the category-search

procedure and those used in subsequent tests was the presence of external features (e.g., hair), and it is likely that this information carries strong orientation cues. It is possible, therefore, that by cropping the external features from our stimuli, we removed head orientation cues and reduced the inversion effects in all regions. If this is the case, our data would suggest that AL is more sensitive to external cues than ML. Whatever the reason, our data show that there are differences between the properties of ML and AL neurons, in agreement with previous work that shows significant differences among these face-selective regions (Freiwald and Tsao 2010).

Although face-selective cells are more frequent in fMRI-defined face-selective regions, single-unit studies have identified also face-selective cells scattered throughout IT (see Bell et al. 2011; Desimone 1991). Also, multivariate pattern analysis fMRI studies in humans (Haxby et al. 2001) and monkeys (Popivanov et al. 2012) show that faces can be distinguished from object categories from activations outside face-category-selective regions. Thus an important question is whether the face neurons outside of the face-selective regions differ in their properties from neurons inside of the face-selective regions or whether the face neurons inside and outside of the face-selective regions are functionally identical and only differ in their degree of clustering. Our results suggest that face neurons outside or inside of the fMRI-defined face regions differ with respect to a behaviorally relevant signature of face perception: face inversion. Only neurons inside of the face-selective regions of IT cortex, and especially in ML, show, as a population, a consistent FIE. The effect of face orientation on neurons outside of the face-selective patches simply depended on a search bias. We cannot exclude that face cells more anterior in IT than where we recorded in the present study, even outside of the most anterior IT face patch, AM, show strong inversion effects for faces that do not contain external features.

The increased overall response to upright compared with inverted faces suggests that an upright face template, which may be driven by biological constraints (Morton and Johnson 1991; Turati et al. 2002) and/or derived from visual experience (Laguesse et al. 2012), is coded in face-selective populations of neurons in ML. This difference in coding between upright and inverted faces is present as early as the initial response burst (90 ms onward) and thus may underlie the perceptual inversion effect in face detection. Usually, the FIE at the behavioral level refers to the considerable drop in the performance of tasks that require the discrimination/matching of faces or the recognition of familiar/learned faces (Laguesse et al. 2012; Yin 1969; see Rossion 2008 for a review). However, the detection of upright faces is also faster and more accurate than for inverted faces. For example, Purcell and Stewart (1986, 1988) asked subjects to detect the presence of faces when stimuli were presented briefly and followed by a mask. Subjects were typically more accurate (and faster to respond) when a face was presented in its canonical orientation compared with an inverted face. Furthermore, if the visual stimulus is degraded (e.g., 2-tone image or "Mooney stimuli"), face detection is largely impaired by inversion (Parkin and Williamson 1987), and face responses are reduced (Andrews and Schluppeck 2004; Kanwisher et al. 1998; Rossion et al. 2011). Picture-plane inversion also impairs and slows down face detection performance in natural scenes (Rousselet et al. 2003) or visual search paradigms (Lewis and Edmonds 2005; VanRullen 2006), especially when the distractors are similar to the target (Garrido et al. 2008).

Our single-cell data thus agree with the idea that neurons in the face-selective regions, especially in ML but not outside of the face-selective regions, underlie the behavioral superior detection of upright compared with inverted faces. This implies that at least one aspect of face processing differs between neurons inside and outside of the face patches, a suggestion that awaits confirmation by direct causal methods.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

J.T., B.R., and R.V. conception and design of research; J.T. performed experiments; J.T., G.V.B., and R.V. analyzed data; J.T., G.V.B., W.V., B.R., and R.V. interpreted results of experiments; J.T. and G.V.B. prepared figures; J.T. and G.V.B. drafted manuscript; J.T., W.V., B.R., and R.V. edited and revised manuscript; J.T., G.V.B., W.V., B.R., and R.V. approved final version of manuscript.

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