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fMRI of the Face-Processing Network in the Ventral Temporal Lobe of Awake and Anesthetized Macaques

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SUMMARY

The primate brain features specialized areas devoted to processing of faces, which human imaging studies localized in the superior temporal sulcus (STS) and ventral temporal cortex. Studies in macaque monkeys, in contrast, revealed face selectivity predominantly in the STS. While this discrepancy could result from a true species difference, it may simply be the consequence of technical difficulties in obtaining high-quality MR images from the ventral temporal lobe. By using an optimized fMRI protocol we here report face-selective areas in ventral TE, the parahippocampal cortex, the entorhinal cortex, and the hippocampus of awake macaques, in addition to those already known in the STS. Notably, the face-selective activation of these memory-related areas was observed although the animals were passively viewing and it was preserved even under anesthesia. These results point to similarly extensive cortical networks for face processing in humans and monkeys and highlight potential homologs of the human fusiform face area.

INTRODUCTION

Face recognition is a critically important cognitive ability for primates, who often communicate with facial expressions and gaze directions and use these cues to determine appropriate behavioral responses. The importance of face processing for social function is illustrated by the effects of prosopagnosia in humans, which can be debilitating (Damasio et al., 1982). Because of the importance of faces, primates have an extensive network of brain areas devoted to face processing (Haxby et al., 2000).

Functional magnetic resonance imaging (fMRI), lesion studies, and electrophysiological studies in humans and monkeys have discovered numerous face-processing areas. In electrophysiological studies in macaques, neurons responding to facial expressions and gaze direction were found in the superior temporal sulcus (STS) (De Souza et al., 2005; Hasselmo et al., 1989; Perrett et al., 1985), while identity is believed to be encoded by neurons in the lateral and anterior ventral temporal cortex (De Souza et al., 2005; Eifuku et al., 2004; Hasselmo et al., 1989; Leopold et al., 2006). Monkey fMRI studies also found multiple face-selective patches, although predominantly in the STS (Bell et al., 2009; Hadj-Bouziane et al., 2008; Logothetis et al., 1999; Pinsk et al., 2005; Tsao et al., 2003, 2008a). In human fMRI studies, activation in the STS is also found, especially in response to facial expressions and dynamic aspects of faces (Haxby et al., 2000), but the fusiform face area (FFA) responds most strongly and with high specificity to faces and is involved in detecting faces (Kanwisher and Yovel, 2006). Comparative fMRI studies (Bell et al., 2009; Hadj-Bouziane et al., 2008; Pinsk et al., 2005; Tsao et al., 2003, 2008a) show correspondence between face-selective activation in monkeys and humans, but substantial differences remain. Differences are particularly pronounced in ventral temporal areas: for instance, little face selectivity has been found in the ventral temporal lobe in macaques and homologs of the FFA or occipital face area (OFA) have not yet been identified.

To date, the degree of overall similarity in face-processing areas between humans and macaques is not clear. Although it is entirely possible that this lack of similarity between humans and macaques is due to species differences, a factor that complicates the question is that fMRI of the temporal lobe is problematic because of the large susceptibility artifacts from the ear canal. In addition, in humans the anterior temporal lobe is often not included in the imaging volume, while the use of surface coils in macaque fMRI can lead to low signal-to-noise ratios (SNR) in ventral areas that are furthest away from the coil. Thus, it is likely that the discrepancy arises because face-selective areas have been missed in humans, macaques, or in both species.

In our earlier work, we showed that by using high-field spin-echo echo-planar imaging (SE-EPI), blood oxygen level-dependent (BOLD) signals can be obtained with high sensitivity in ventral temporal areas despite the presence of susceptibility gradients from the ear canal and that SE-based fMRI outperforms gradient echo (GE) fMRI in these regions (Goense et al., 2008). Here, our goal was to map the face-selective network in macaques, particularly in the ventral temporal lobe. As stimuli we used monkey faces with different views,

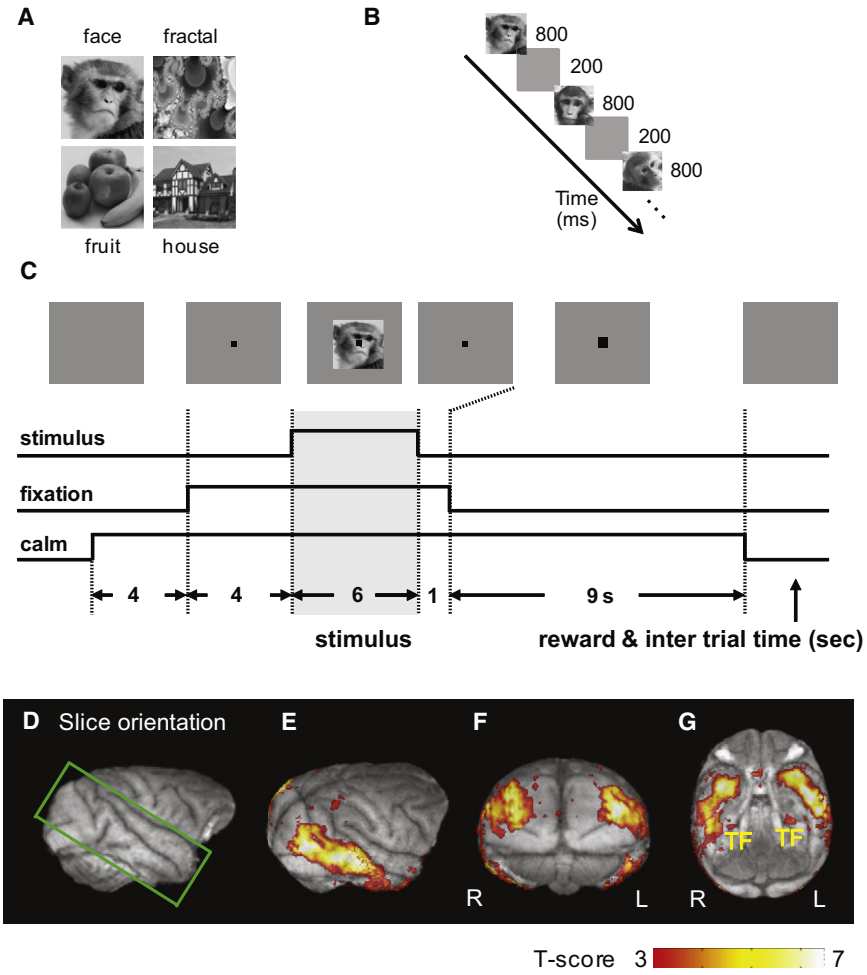

Figure 1. Experimental Paradigm and Example Stimuli for Each Object Category

(A) Example images for faces, fruit, houses, and fractals. All images have the same mean intensity and contrast and similar power spectrum.

(B) Images were randomly selected from a category and presented for 800 ms with a 200 ms blank (isoluminant gray) in between.

(C) Behavioral paradigm for experiments with awake animals. The monkey initiated a trial by ceasing body and jaw movement and was required to remain motionless throughout the trial. Four seconds after the start of the trial a fixation spot was shown, upon which the monkey was required to fixate in a 3° window. After 4 s of fixation the stimulus was presented. The monkey maintained fixation during stimulus presentation and for an additional second afterwards. After this the monkey was allowed to break fixation but needed to remain immobile for 9 more s. The monkey received a juice reward after successfully completing the trial.

(D–G) Visually responsive areas in an awake monkey (B04, all categories versus blank). In awake fMRI-experiments the entire temporal lobe and part of the parietal lobe were covered (D). (E–G) Visually responsive voxels are shown on a rendered brain ($p < 0.001$ uncorrected, cluster-level ≥ 5). Visual activation can be seen in the entire temporal lobe. The ventral view in (G) shows extensive activation in the temporal lobe without loss of BOLD signal near the ear canal. Because the extent of the stimuli was 5°, V1 activation (E and F) was restricted to the foveal 5°.

expressions, and gaze directions to activate areas that respond to identity as well as areas that respond to social cues like facial expression. Faces were contrasted against fruit, houses, and fractals. In addition, we repeated the experiment in anesthetized monkeys to eliminate possible confounding effects of motion and to identify those areas that depend on awake processing.

We found face-selective patches in STS, prefrontal cortex, and amygdala in agreement with earlier fMRI studies in the macaque (Logothetis et al., 1999; Pinsk et al., 2005; Rajimehr et al., 2009; Tsao et al., 2003, 2008b). But we also found face selectivity in several additional locations: ventral V4, anterior TE, and the parahippocampal cortex in the ventral temporal lobe and the hippocampus and entorhinal cortex (EC) in the medial temporal lobe (MTL). The face-selective pattern was largely similar in awake and anesthetized monkeys, suggesting that most of this network is not dependent on the awake state of the animal. Our results show that the face-processing network in the macaque brain is more extensive than reported previously and includes several additional areas in MTL and the ventral temporal cortex, including potential FFA homologs.

RESULTS

Visual Responses in the Temporal Lobe

fMRI data from two awake and three anesthetized monkeys were acquired while the animals were shown visual stimuli belonging to different categories (faces, fruit, fractals, and houses for awake animals and faces and fruit for anesthetized animals). Data were acquired at 7T by using a vertical primate scanner (see Goense et al., 2008 for technical details). Figure 1 shows examples of the stimuli (Figure 1A) and the timing of the behavioral paradigm used for awake monkeys (Figures 1B and 1C). We used an SE-based functional imaging protocol that was optimized to perform fMRI in the ventral temporal lobe and was previously shown not to suffer from signal loss near the ear canal (Goense et al., 2008). Figures 1D–1G show that by using this protocol we were able to reliably record functional activation in the ventral temporal lobe. Figures 1E–1G show visually induced functional activation in an awake animal in response to static images. Visual responses were found in the early visual cortex (V1–V4) and in a large portion of the temporal cortex, including the STS and inferior temporal gyrus (ITG). In addition, the ventral temporal cortex was also clearly activated (Figure 1G), including

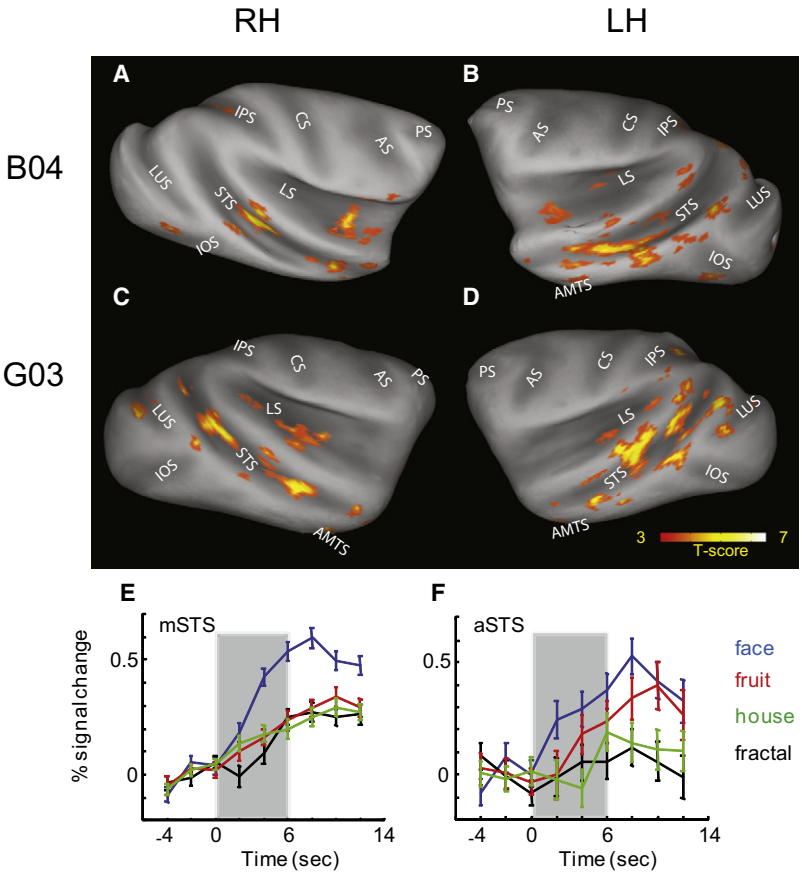

Figure 2. Brain Areas in the STS and ITG that Showed Significantly Higher Responses to Faces Than to the Other Categories in Two Awake Monkeys

(A–D) Face-selective areas shown on 3D reconstructed brains. The right hemispheres are shown in (A) and (C) and the left hemispheres in (B) and (D). Face-selective activity is seen in the STS, fundus, upper and lower bank, and the lip. The most extensive face-selective activation was found bilaterally in the middle and the anterior STS. Contrast: face > fruit, house, and fractals; $p < 0.001$ uncorrected, cluster-level ≥ 5 voxels.

(E and F) Average time courses of the face patches in the middle (mSTS) (E) and anterior STS (aSTS) (F) of monkey B04 in response to the different categories. The time courses show that the face patches in the STS also responded to the other categories. The time courses represent the average responses over the significantly activated voxels in the middle and anterior STS. The gray area indicates the stimulus duration. Error bars show the SEM. See Figure S1 for coronal views of the face-selective areas in STS. Abbreviations: AMTS, anterior medial temporal sulcus; AS, arcuate sulcus; CS, central sulcus; IOS, inferior occipital sulcus; IPS, intraparietal sulcus; LS, lateral fissure; LUS, lunate sulcus; PS, principal sulcus.

ventral TE and the parahippocampal region (area TF). The pattern of visually elicited activation agrees well with the known visual areas based on electrophysiological and anatomical data (Gattass et al., 2005).

Face and Object Selectivity in the STS

We examined face-selective areas in the STS and ITG of awake monkeys (Figure 2) with the purpose of comparing the functional activation measured with the high-field SE-BOLD method to data reported in the literature with the more common GE-BOLD method (Pinsk et al., 2005) and the contrast agent-based cerebral blood volume (CBV) method (Tsao et al., 2003, 2008a). The comparison of faces versus the other three object categories yielded significant bilateral face-selective BOLD activation in the anterior, middle, and posterior parts of the STS (Figure 2 and Figure S1, available online). All animals showed strong and extensive face-selective activation in the STS (Table 1) in agreement with previous studies in macaques (Logothetis et al., 1999; Pinsk et al., 2005; Rajimehr et al., 2009; Tsao et al., 2003, 2008a). Although in cases of strong activation the STS middle patch appeared to be contiguous, single-subject analysis showed that in several animals it actually consisted of two separate patches. Figures 2E and 2F show the time courses of the signals in the anterior and middle face patches in the STS of monkey B04. The face patches showed significantly higher responses to faces than to the other categories, but they showed nonzero responses to the other object categories. These results indicate that the face areas in the STS do not exclusively respond to faces, consistent with previous literature in humans and monkeys (Bell et al., 2009; Haxby et al., 2001; Ishai et al., 1999; Pinsk et al., 2005; Tsao et al., 2003). Because STS neurons respond selectively to different categories, including faces and other objects (Logothetis and Sheinberg, 1996; Zangenehpour and Chaudhuri, 2005), we also examined the object selectivity in the STS by comparing the response to each of the nonface categories to the other three categories. By using the same criteria as for face-selective regions, we found that fruit evoked higher BOLD responses than the other categories in several brain regions across all subjects (Figure 3 and Table S1). Fruit-selective activation was found in V3, the posterior STS (TEO), and anterior STS (IPa). Fruit-selective activation in the STS was located at AP 12 to 20 and AP –5 to –1, just posterior to the face-selective patches. The distribution of house- and fractal-selective voxels was not consistent across animals, which suggests that only biologically relevant objects such as faces and fruit evoke sufficiently strong and clustered functional activation in the monkey temporal cortex.

Face Selectivity in the Ventral Temporal Cortex

Although many electrophysiological studies have shown face- and object-selective cells in the anterior temporal pole in macaques (i.e., area TGa, the area around the anterior medial temporal sulcus [AMTS], and the perirhinal and entorhinal cortices; Nakamura and Kubota, 1996) and fMRI activation has been shown in monkeys (Logothetis et al., 1999; Tsao et al., 2003) and humans (Kriegeskorte et al., 2007; Rotshtein et al., 2005), face-selective BOLD signals are not always strong or

Table 1. Face-Selective Areas in Awake and Anesthetized Monkeys

	Awake		Anesthetized		
	B04	G03	N08	L04	C06
Known Face Areas					
AMTS (TEav)[a]	R	BA	BA	BA	BA
aSTS[a]	BA	BA	L	BA	BA
mSTS[a]	BA	BA	BA	BA	BA
Amygdala	BA	L	BA	–	–
OF	*	*	L	BA	BA
PF	*	*	BA	BA	BA
Unknown Face Areas					
vV4[a]	L	BA	BA	BA	R
mTF[a]	BA	R	BA	L	BA
Entorhinal cortex[a]	R	L	R	BA	BA
aInsula (or LS)[a]	BA	BA	L	BA	L
pCingulate (area 23/24)[a]	BA	BA	BA	BA	BA
vTE (TEpd)[b]	R	L	BA	L	–
TGa[b]	R	L	BA	BA	–
pInsula[b]	R	R	R	R	–
aCingulate (area 32)[b]	*	BA	BA	BA	BA
aHippocampus	BA	BA	R	–	–
mHippocampus	BA	BA	L	–	–
Claustrum	*	*	BA	BA	L
vaTE (TEad)	L	–	R	BA	–

Included in the table are all areas that showed significantly higher responses to faces than to the other categories in at least three monkeys ($p < 0.001$ uncorrected; cluster-level ≥ 5 voxels). Most areas showed bilateral activation (BA), although several areas showed lateralized responses (indicated L for the left and R for the right hemisphere). *Brain areas that were not included in the imaging protocol (prefrontal areas and anterior cingulate) or for which the resolution was insufficient to accurately delineate them (claustrum).

[a]Areas where face-selective activity was found in all animals.

[b]An area was activated in four out of five monkeys.

reproducible in this region (Rajimehr et al., 2009). This is probably due to signal loss caused by the strong susceptibility gradients in the ventral temporal lobe. The susceptibility artifacts from the ear canal can potentially obscure face-selective areas in the ventral temporal lobe in both humans and monkeys. Hence, a goal of the present study was to examine whether there are possibly additional face-selective areas in this region. By using our SE fMRI protocol, we found multiple face-selective areas in the ventral temporal cortex and MTL in both awake monkeys (Figure 4 and Figure S2). We considered an area face selective if it was significantly activated in four or all five animals (see Table 1); although activation was often bilateral, bilateral activation was not required for inclusion. We found face-selective areas around the AMTS (labeled AMTS) at AP 17–21 (Figure 4B), which for four animals was localized in TEav, and for one at the border of TEav and TEad. Furthermore, a face-selective area was found in anterior ventral TE (AP 13–21) corresponding to TEad and another patch was found in the most anterior part of the temporal cortex, area TGa (Table 1). In addition, we also observed face-selective activation in ventral V4 near TF (Figure 4C, Figures S2C and S5, and Table 1), and a face-selective area located in the parahippocampal cortex (area TF) at AP 2–10 (Figure 4D, Figures S2D and S5, and Table 1). The location and size of the latter two activated areas are given in Table S2. Our results indicate that the ventral temporal cortex contains multiple additional face-selective patches.

Although the monkeys were only required to fixate, we found face-selective activation in the medial temporal lobe in the entorhinal cortex (Figure 4E and Figure S2E) and two patches in the hippocampus (anterior and posterior) (Figure 4G and Figure S2G), areas usually associated with memory (Squire et al., 2004). Face-selective activation was also identified in the amygdalae in both awake monkeys (Figure 4F and Figure S2F) in agreement with previous fMRI and neurophysiology studies (Hadj-Bouziane et al., 2008; Hoffman et al., 2007; Leonard et al., 1985). Outside the temporal lobe, face-selective patches were found in the anterior insula (Figure 4H and Figure S2H) and posterior cingulate cortex (Figure 4I and Figure S2I).

Face Selectivity in Awake and Anesthetized Monkeys

Three monkeys were scanned anesthetized, with the goal of identifying whether activation of these face-selective areas depends on processes that require the animal to be awake, like processes involving attention or memory. Because even minor animal motion can potentially lead to artifactual activation (Goense et al., 2010), anesthetized experiments have an additional advantage in that they provide a control, which allowed

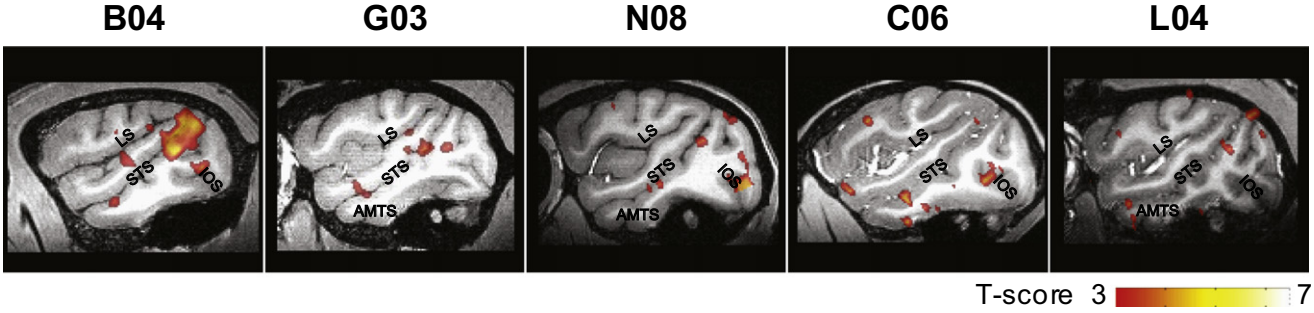

Figure 3. Brain Areas Selective to Fruit

Fruit-selective areas are located in the STS, the ITG, and the IOS. See also Table S1. Contrast: fruit > face, house, and fractals in the awake animals B04 and G03, and fruit > face in anesthetized animals; $p < 0.001$ uncorrected, cluster-level ≥ 5 voxels.

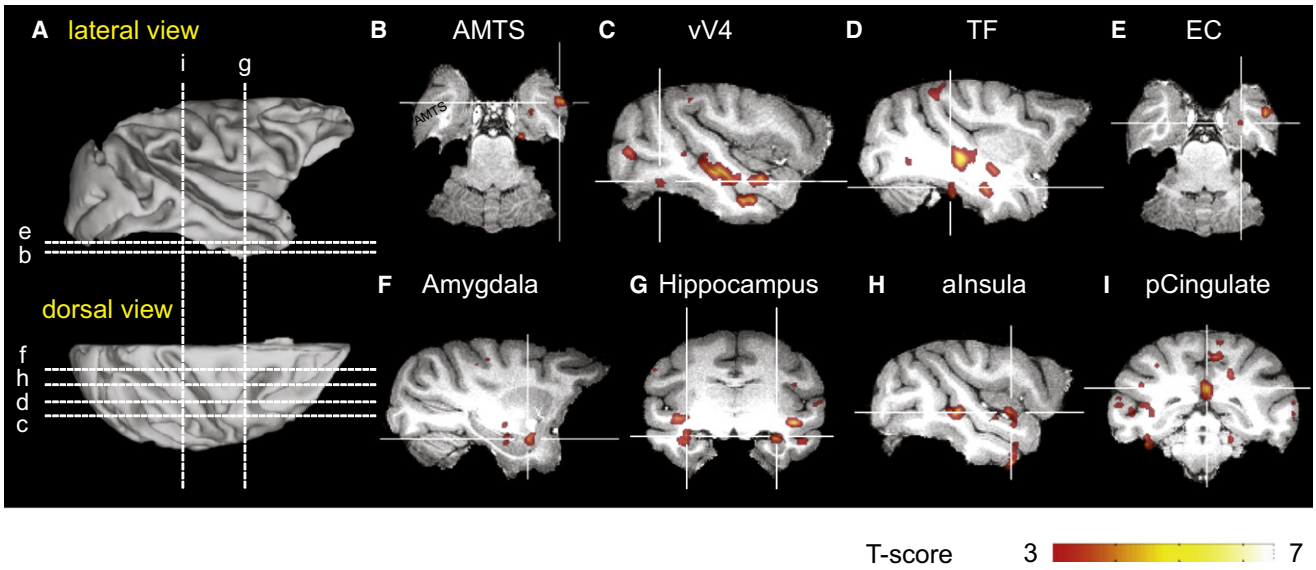

Figure 4. Face-Selective Areas in Awake Monkey B04

(A) Locations of the slices shown in panels (B–I).

(B–I) Face-selective areas were found around AMTS (B), ventral V4 (C), area TF (D), the entorhinal cortex (EC; E), the amygdala (F), the anterior hippocampus (G), the anterior insula (aInsula; H), and posterior cingulate cortex (pCingulate; I). Also visible are the face-selective patches in the entorhinal cortex (B), the STS (C, D, and G–I), around the AMTS (E and H), the hippocampus (F), and area TF (I). The activated areas showed significantly higher responses to faces than to the control categories (face > fruit, houses, and fractals; $p < 0.001$, cluster-level $\geq$ 5 voxels). See Figure S2 for the other awake monkey.

us to verify that areas found in awake monkeys were not contaminated by motion artifacts.

Figure 5 shows that face-selective responses in most areas were retained under anesthesia and the pattern of activity was largely similar for awake and anesthetized animals. Figure S3 shows the other two anesthetized animals and Table 1 provides a summary of the areas that were activated in the two awake and three anesthetized monkeys. Face-selective functional activity was preserved under anesthesia in the STS (Figure S4), in the ventral temporal lobe, around the AMTS, and in ventral V4, area TF, the entorhinal cortex, the insula, and cingulate cortex (Figure 5, Table 1, and Figures S3 and S5).

In contrast to the awake animals, where we focused on the temporal lobe, in anesthetized animals the entire brain was scanned. Thus, we also found two face-selective areas in the prefrontal cortex (Table 1): one in the lower limb of the arcuate sulcus (area 44/45, Figure S4) and one in the orbital frontal (OF) cortex (area 13 m). Prefrontal face-selective activation has been identified previously by using fMRI in anesthetized (Logothetis et al., 1999) and awake macaques (Tsao et al., 2008b).

The notable differences between awake and anesthetized monkeys occurred in the hippocampus and amygdalae. Responsiveness to faces was detected in the amygdalae of both awake monkeys but only in the amygdala of one anesthetized monkey (Table 1). Hippocampal activation, which was bilateral in both awake monkeys, was absent in two of the anesthetized monkeys and unilaterally preserved in one animal. The functional activation in the amygdalae and hippocampus is

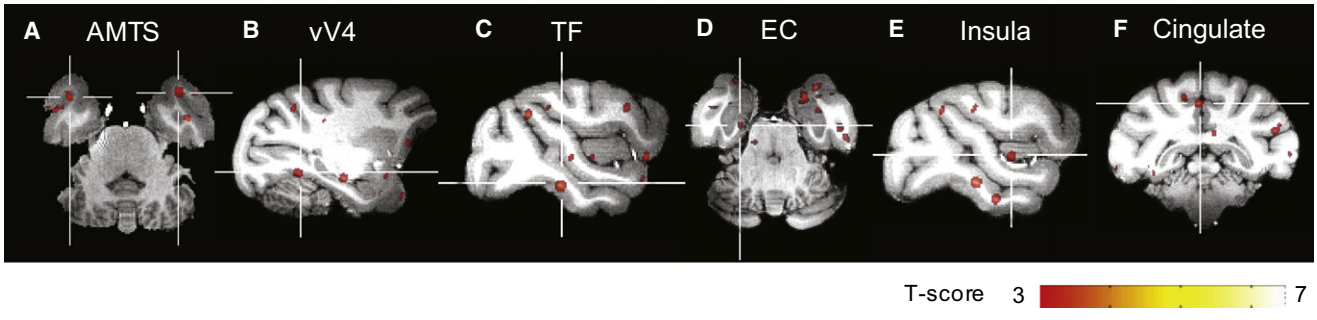

Figure 5. Face-Selective Areas in a Representative Anesthetized Monkey

The AMTS area (A), ventral V4 (B), area TF (C), the entorhinal cortex (D), the insula (E), and the posterior cingulate cortex (F) are also activated in anesthetized monkeys (face > fruit; $p < 0.001$ uncorrected, cluster-level $\geq$ 5 voxels). Also visible are the hippocampus and the orbital frontal cortex (B), the STS and insula (C), the amygdala (D), and the STS (E). See Figure S3 for the other two anesthetized animals.

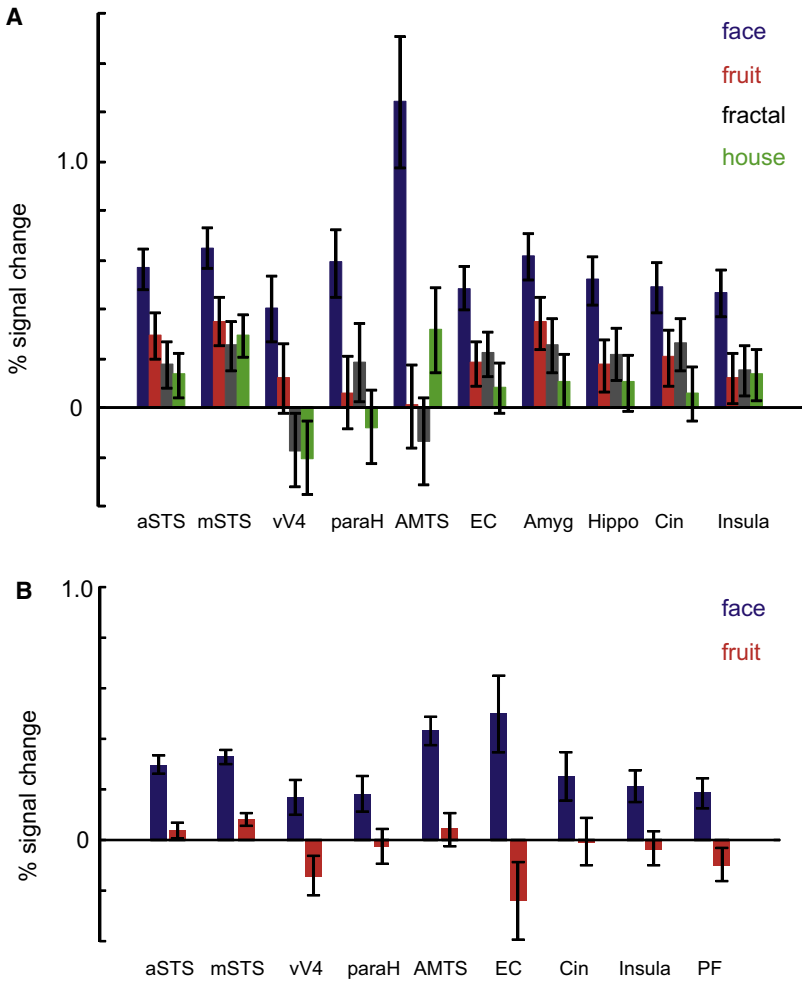

Figure 6. Percentage BOLD Signal Change of the Face-Selective Areas in Response to the Different Stimulus Categories

(A and B) Mean responses to the different categories for awake monkeys (A, two monkeys) and anesthetized monkeys (B, three monkeys).

(A) For awake monkeys the mean response amplitude was determined by calculating the percentage change at the peak response (6–10 s after stimulus onset) over all significantly activated voxels of a given patch and averaged across animals and experiments. Only the middle STS showed significant responses to all control categories. The responses to fruit, houses, and fractals in the face-selective areas in awake monkeys were not significantly different from each other and thus only fruit was used as a control in the anesthetized experiments.

(B) The response amplitudes were lower than in awake monkeys but selectivity patterns were similar. Only the middle STS showed a significant response to fruit. Error bars indicate the SEM. Abbreviations: paraH, parahippocampal cortex; Amyg, amygdala; Hippo, hippocampus; Cin, cingulate; PF, prefrontal cortex.

suppressed under anesthesia or at the least severely reduced. That these areas are activated only in awake animals suggests they are involved in awake processing of faces or their properties.

Figure 6 shows the mean responses of the face-selective areas to faces and to the other categories in awake and anesthetized animals. Overall response amplitudes were lower in anesthetized than awake monkeys. The reduction of the amplitude of the BOLD signal was expected given the effects of anesthesia on the vascular system. While the face-selective areas in the middle STS showed significant responses to the other object categories (t test, $p < 0.05$), the ventral areas, for instance near the AMTS, were more selective to faces, given that the responses to objects were often not significantly different from zero in these areas. These results suggest that the ventral pathway is more selective for faces than the STS patches.

DISCUSSION

In this study, we took advantage of the increased sensitivity of high-field (7T) SE fMRI to study face processing in the temporal lobe of awake and in the entire brain of anesthetized monkeys. First, we confirmed the face-selective activation found in earlier monkey fMRI studies, but in addition, we found and report a number of face-selective areas in the ventral and medial temporal lobe that have not been described before, such as ventral V4, ventral TE, TG, hippocampus, entorhinal cortex, and parahippocampal cortex (area TF). Some of the more posterior areas may be homologous with human occipitotemporal face areas. We also scanned awake and anesthetized animals by using the same protocol and observed that MTL activation that was present under passive viewing was mostly preserved under anesthesia (except in the hippocampus), suggesting that processes related to memory, like familiarity or recollection, are not necessarily required for functional activation in the MTL.

Face-Selective Activation in the Temporal Lobe

In agreement with previous studies of face-selective activation in macaques we found extensive face-selective activation in STS, with the largest and most reproducible face-selective patches located in the middle STS, which responded to other categories as well (Pinsk et al., 2005; Tsao et al., 2003). Activation in or near the AMTS was also found in all animals and was highly specific to faces. Selectivity of AMTS areas for faces was also identified in earlier fMRI studies (Logothetis et al., 1999; Tsao et al., 2003) although not in all, most likely because of signal loss in the temporal lobe. Additional face-selective areas were found in area TG and ventral TE but these results were less reproducible across animals. Figure 7 summarizes our results and compares them to the face-selective areas that were previously reported by using macaque fMRI (Bell et al., 2009; Logothetis et al., 1999; Pinsk et al., 2005; Tsao et al., 2008a, 2008b). The figure highlights the overall agreement across studies and illustrates the interindividual variability. Note that in our study faces with

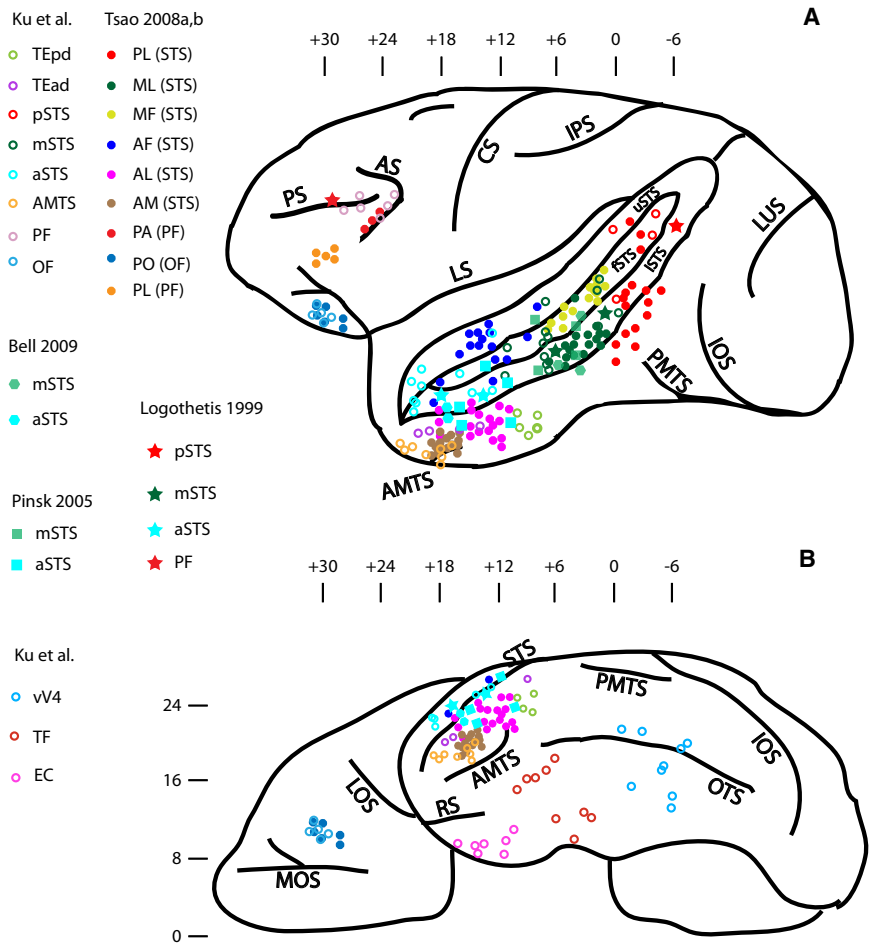

Figure 7. Comparison of Face-Selective Activation Found in the Current Study with Face-Selective Activation Described in the Literature Superimposed on a Side and Ventral View of the Brain

(A) Side view of the brain. The locations of face-selective patches found in the literature (Bell et al., 2009; Logothetis et al., 1999; Pinsk et al., 2005; Tsao et al., 2008a, 2008b) are marked by closed symbols and locations found in the current study are indicated by the open circles. For the activated areas described by Tsao et al. (2008a, 2008b), naming conventions used by the authors were retained with the locations in parentheses. Locations were estimated based on AP positions when given; otherwise positions were estimated by comparing the coronal slices to the atlas by Saleem and Logothetis (Saleem and Logothetis, 2006). In cases where activation extended over multiple slices the average position was taken. The locations shown are after normalization to the macaque template (McLaren et al., 2009). Note that not all studies (including ours) make a distinction between STS patches located on the lip and the fundus.

(B) Ventral view of face-selective activation in this study (open circles) and the literature (closed symbols). The coordinates of the ventral activation are given in Table S2. Abbreviations: LOS: lateral orbital sulcus; MOS: medial orbital sulcus; OTS: occipitotemporal sulcus; PMTS: posterior middle temporal sulcus; RS: rhinal sulcus.

different gaze directions and expressions were used, while other investigators used neutral faces, which may account for some of the observed variability, especially in STS. Electrophysiological data in monkeys show that STS neurons encode facial expressions and gaze directions, and face-selective neurons in the anterior ventral temporal cortex are thought to be involved in the encoding of identity (De Souza et al., 2005; Eifuku et al., 2004; Hasselmo et al., 1989; Leopold et al., 2006). Human fMRI data show a similar division, with the STS being involved in the encoding of changeable aspects of faces, while ventral and anterior areas are involved in detecting faces and encoding identity (Haxby et al., 2000; Kriegeskorte et al., 2007; Rotshtein et al., 2005; Sergent et al., 1992).

Because the SE signal is not degraded by susceptibility artifacts from the ear canal and because we used volume coils that provided uniform SNR in the entire ventral visual pathway, it allowed us to map several additional face-selective patches in ventral areas (Figure 7B). We found face-selective patches in the posterior part of the ventral temporal cortex, of which the most posterior patch was located in the anterior part of ventral V4. Face selectivity in this area has not been reported before, but most electrophysiological studies in this region used simple features such as gratings, edges and textures, and selectivity to complex objects such as faces was not explicitly tested (Gattass et al., 1988). We assigned the activation in this area to ventral V4 based on the histological atlas by Saleem and Logothetis (Saleem and Logothetis, 2006). However, this area is not very well studied with electrophysiology and the border of ventral V4 also shows substantial interanimal variation (Boussaoud et al., 1991; Gattass et al., 1988). Furthermore, different atlases show variation in the areal borders in this region (Paxinos et al., 2000; Saleem and Logothetis, 2006). Because activation was often located near the border of V4 it also cannot be excluded that activation was located adjacent to ventral V4. Thus, to be able to definitively assign this activation to ventral V4, the location would have to be verified histologically in the same animal. So although this face-selective area might be a tentative homolog of the OFA in humans, which is located adjacent to human V4 (Brewer et al., 2005; Hasson et al., 2003), it requires further study. Face-selective activation was also found in all animals in area TF, which lies anterior to ventral V4 and is part of the parahippocampal cortex. According to anatomical and retinotopic criteria, Halgren et al. (Halgren et al., 1999) predicted that a macaque homolog to the human FFA would be located in this area. Responses to objects have been reported with electrophysiology in area TF (Boussaoud et al., 1991; Riches et al., 1991; Rolls et al., 2005) and neurons that exhibited some response to faces were seen in the parahippocampal cortex (Sato and Nakamura, 2003), although the parahippocampal cortex is usually associated

with spatial processing (Alvarado and Bachevalier, 2005; Bachevalier and Nemanic, 2008). However, this region is still relatively unexplored with electrophysiology and except for the current study no fMRI study has yet shown face-selective activation in macaque parahippocampal cortex.

All in all, some of the above-mentioned areas may be homologs of the OFA and FFA in humans. Further study is needed to determine whether these or any of the other areas found in the macaque are actual homologs of human face areas. Similar activation and functionality for anterior ventral areas between macaques and humans has been suggested (Tsao et al., 2008a), but a macaque equivalent of FFA has not been conclusively identified. Face-selective activation in the fusiform gyrus was also shown in chimpanzees (Parr et al., 2009). Because the middle STS patch shows the strongest and most robust activation in monkeys, as FFA activation is most robust in humans (while STS activation is often weak), the middle STS patch was suggested to be the macaque equivalent of FFA, which was supported by similarity after warping the brain maps of macaques and humans (Orban et al., 2004; Rajimehr et al., 2009; Tsao et al., 2003, 2008a). However, STS in humans is involved in processing of gaze direction and expression as well (Puce et al., 1998; Winston et al., 2004), suggesting functional similarity between humans and monkeys. The intensity difference may reflect different specialization and different emphasis between the species, i.e., possibly a stronger emphasis on detection and identification in humans and a stronger emphasis on expression in monkeys. Thus, the homology question requires further study. Comparative studies between macaques and humans are likely to benefit from performing SE fMRI of the more anterior ventral temporal areas in humans. Although Schmidt et al. (Schmidt et al., 2005) found that SE fMRI revealed no additional face-selective areas, their study was performed at 3T, and because functional changes are lower for SE-BOLD than for GE-BOLD methods, the BOLD signal may not have been sufficient to show significant activation. Also, small face-selective areas are easily missed if the spatial resolution is insufficient (Op de Beeck et al., 2008). The higher BOLD signal and the higher spatial resolution achievable at high field (7T) may negate some of these drawbacks and may reveal additional face-selective areas in humans as well.

Effects of Anesthesia

There was a large degree of similarity in the areas that were activated in awake and anesthetized monkeys. Most visual areas also showed face selectivity under anesthesia, including prefrontal areas. The difference in stimulus size between awake and anesthetized animals did not lead to any differences between awake and anesthetized animals, most likely because faces were contrasted against other categories and because many of the reported areas are size invariant. The areas that showed no consistent activation under anesthesia were the amygdala and the hippocampus. Both awake animals showed bilateral activation in the amygdala, in agreement with earlier studies (Hadj-Bouziane et al., 2008; Hoffman et al., 2007). Only one animal showed activation in the amygdala under anesthesia. However, face-selective responses may not have reached significance in the anesthetized monkeys, because faces were contrasted against fruit and the amygdala also showed significant responses to fruit in awake monkeys ($p < 0.05$). The amygdala has a high μ-opioid receptor density (Mansour et al., 1988) and it is also possible that binding of remifentanil may have reduced its neural responses.

There are two caveats concerning the results from anesthetized monkeys. One is that the results may depend on the type of anesthesia and results may not generalize to other anesthesia regimens because different anesthetics affect cognitive processing differently. The other concerns the interpretation of the BOLD signal. It has been shown in V1 that the BOLD signal better represents the input to an area and its local processing than its output and that functional activation can occur in the absence of spiking (Goense and Logothetis, 2008; Logothetis et al., 2001). The conservative interpretation of preserved BOLD signal in a brain area would be that this means the activated area receives synaptic input. What types of further neural processes take place, whether these differ between awake and anesthetized animals, and how they relate to single- or multiunit electrophysiological data (neural output) remains subject to further investigation. Conversely, a lack of BOLD signal could signify a lack of input from an earlier area. The issue of interpretation of the BOLD signal is independent of anesthesia, however, and is also relevant for awake subjects.

Face-Selective Activation in the MTL

The importance of the MTL in learning and memory function is well established. Area TE, the perirhinal (Brodmann areas 35 and 36) and parahippocampal cortices, the entorhinal cortex, and the hippocampus have all been shown to be involved in learning and memory (Osada et al., 2008; Squire et al., 2004) with different structures mediating different (and possibly overlapping) functions, i.e., forming associations between objects, forming associations between objects and locations, or forming memories of scenes or locations. Although face selectivity is usually not explicitly tested, neural and BOLD responses to faces were shown in the human MTL in the context of memory and familiarity (Eichenbaum et al., 2007; Gonsalves et al., 2005; Quiroga et al., 2005). We found face-selective activation in the ventral areas TE and TG, but also in MTL structures, including the hippocampus, entorhinal cortex, and parahippocampal cortex, even though the monkeys were passively viewing. Activation in the parahippocampal and entorhinal cortex and areas TE and TG also remained under anesthesia.

Two intensely debated questions are: (1) whether the MTL serves only a memory function or whether it also has a role in visual perception (this concerns in particular the perirhinal cortex; Baxter, 2009; Gaffan, 2002; Graham et al., 2010; Levy et al., 2005; Suzuki, 2009) and (2) whether familiarity and recollection are mediated by different MTL structures (this question focuses on whether the hippocampus is also involved in familiarity; Eichenbaum et al., 2007; Squire et al., 2007). Because our animals were not engaged in a memory task we cannot directly address such questions, albeit the activation of MTL structures under passive viewing and anesthesia may provide important hints on them. There are several possible interpretations of the activation of the MTL under passive viewing and anesthesia: (1) the BOLD signal in these areas reflects visual input, but cannot be directly associated to the function or the

output of the area; (2) MTL neurons respond to the visual properties of the stimuli (this would argue for a perceptual involvement of the MTL); (3) activation is due to familiarity or memory, with faces as a preferred stimulus, although this would imply that these processes take place under anesthesia.

Although the stimuli were familiar to the awake animals, two of the anesthetized animals had never seen the stimuli before. Thus, face-selective responses in the entorhinal and parahippocampal cortex in these animals cannot represent prior memory or familiarity of the stimuli. Although the assumption that familiarity or memory processes play absolutely no role under anesthesia is difficult to prove, it is likely that they are eliminated or suppressed under anesthesia. However, this would imply that activation in the anterior temporal lobe, the entorhinal cortex, and the parahippocampal cortex is due to passive processes reflecting the tuning of neurons to visual properties of the stimulus or due to input from earlier areas. Functional activation of the hippocampus was reduced under anesthesia (activation was unilaterally preserved in only one animal), suggesting that the hippocampus may need processes like storage and retrieval to be activated.

The MTL may show face-selective activation given the biological relevance to macaques. Identification of conspecifics and their association to certain events is important for monkeys' social functioning and the MTL may play an important role in encoding and retrieval of information associated with specific individuals. Although the MTL activation found in this study raises many interesting questions, further study with memory tasks is needed to address these questions.

In conclusion, by using high-field SE fMRI, we were able to show functional activation in an extensive network within the ventral temporal lobe and MTL and identified several additional face-selective areas, some of which may be homologous to human face areas. Most activated areas were also activated under anesthesia, suggesting the network is to a large extent independent of conscious processes.

EXPERIMENTAL PROCEDURES

Subjects

Awake monkey fMRI experiments were performed on two healthy male monkeys (*Macaca mulatta*), weighing 14 (G03) and 16 kg (B04). We needed three experimental sessions for animal B04 and five sessions for animal G03. In each session, the monkey successfully performed the task for an average duration of 2 hr. All experiments were approved by the local authorities (Regierungspräsidium) and were in full compliance with the guidelines of the European Community (EUVD 86/609/EEC) for the care and use of laboratory animals. The primate setup and hardware for the awake monkey experiments were described in detail previously (see Goense et al., 2008 and Logothetis et al., 1999). Briefly, the monkeys were implanted with a custom-made MR-compatible headpost and extensively trained in a mock environment to acclimatize them to the scanner environment and noise. During scanning the monkeys were seated in a custom-made primate chair with their head fixed to a predetermined location on the chair to ensure reproducible positioning in each session. The animal's jaw and body motions were monitored by custom-designed sensors. Eye movements were monitored by using an infrared camera or implanted eye coil and data were analyzed with iView software (iView, Sensomotoric Instruments GmbH, Teltow, Germany). Anesthetized experiments were performed on three adult macaques weighing 7–12 kg (two males, C06 and L04, and one female, N08). The experimental setup and anesthesia protocol were similar to the procedures described in Logothetis et al., 1999. Anesthesia was maintained with remifentanil (0.5–2 μg/kg/min) and mivacurium chloride (3–6 mg/kg/hr). Physiological parameters were monitored and maintained within the normal physiological range as described previously (Logothetis et al., 1999).

Visual Stimulation

In awake experiments visual stimuli were presented binocularly by using an SVGA fiber optic system (AVOTEC, Silent Vision) with a resolution of 800 × 600 pixels and frame rate of 60 Hz. The stimuli were 24 exemplars of faces, fruit, houses, and fractals (Figure 1A) and occupied 5° × 5° of visual angle. The smaller stimuli made it easier for the monkeys to maintain fixation. Images were black and white, normalized to the same mean intensity and contrast, and overlaid on a gray background with the same intensity as the mean intensity of the stimuli. All stimuli had similar power spectra. Fractals were used instead of scrambled images because the power spectra of fractals more closely match that of natural objects (Falconer, 2003). The face stimuli were monkey faces of different individuals and although the individuals pictured were unknown to the monkeys they were trained on these exemplars. The monkey faces had different views, gaze directions, and facial expressions. Figure 1C shows the trial-based behavioral paradigm that was used to obtain artifact-free MR images. Trials were initiated by the monkey by ceasing body and jaw motion. After sitting quietly and fixating on a central fixation spot for 4 s, six images were presented (Figure 1C). The animals were required to fixate within a 3° window before and during the stimulus. To receive the reward, the monkeys had to remain motionless for an additional 9 s. Trials were aborted when the animal moved or broke fixation.

In anesthetized experiments, the stimuli were presented by using a custom-made MR-compatible display system, similar to the AVOTEC system, with a resolution of 800 × 600 pixels. Animals were wearing lenses (Wöhlk-Contact-Linsen, Schönkirchen, Germany) to focus the eyes on the stimulus plane and the eyepieces of the stimulus presentation system were positioned by using a modified fundus camera (Zeiss RC250; see Logothetis et al., 1999). The same stimuli were used as in the awake experiments except that a block-design paradigm was used and stimuli spanned 10° × 10°. Only faces and fruit were used in the anesthetized experiments because the responses of the face-selective areas to the control categories were not significantly different in the awake experiments. In anesthetized monkeys larger stimuli were used to decrease possible errors because of minor variations in the alignment of the displays to the center of the fovea. Given that the face stimuli are contrasted against fruit and size differences affect both categories, stimulus size is not expected to affect the results. In each block, 48 images were presented in random order (24 exemplars of the same category, each presented twice), yielding a 48 s visual stimulation time. During the blank period a mid-gray square was presented for 48 s.

MRI

Images were acquired by using a 7T vertical Bruker BioSpec scanner with a bore diameter of 60 cm (Bruker BioSpin, Ettlingen, Germany). The imaging procedure for awake monkeys was described in detail elsewhere (Goense et al., 2008); a summarized description follows. The RF coil was a custom-made 16 cm saddle coil that covered the entire brain and was optimized for imaging of the temporal lobe. A two segment SE-EPI was used for image acquisition. The field of view (FOV) was 12.8 × 9.6 cm^2 and the matrix size was 84 × 64 for B04 and 96 × 64 for G03. Slices were 2 mm thick and were acquired at −20° from the Frankfurt zero plane (Figure 1D) to reduce susceptibility artifacts. Seventeen slices per volume were used to cover the entire visual cortex. TE was 40 ms and TR 1 s, yielding a final temporal resolution of 2 s per volume. A total of 3440 volumes were used in the analysis for B04 and 4563 volumes for G03. For anatomical reference a high-resolution (0.5 mm isotropic) T_1-weighted three-dimensional (3D) MDEFT image was acquired under general anesthesia at 4.7 T (see Logothetis et al., 1999). In each session, SE-EPI and GE anatomical reference images were acquired with the same slice orientation as the functional images. For the GE anatomical reference, which was used for quick visualization during experiments, FOV was 12.8 × 9.6 cm^2, matrix size 256 × 256, slice thickness 1 mm, TE 10 ms, and TR 750 ms. For the SE-EPI anatomical reference, which was used as an intermediate to accurately coregister the statistical map with the MDEFT image, a 16 segment SE-EPI was acquired (see Goense et al., 2008). The

matrix was 256 × 192, bandwidth 60–159 kHz, spatial resolution 0.5 × 0.5 mm^2, slice thickness 1 mm, TE 62 ms, and TR 4 s. For field mapping, two 3D FLASH images were acquired with FOV 12.8 × 9.6 × 9.6 cm^3 and matrix 128 × 128 × 64, resulting in a resolution of 1 × 0.75 × 1.5 mm^3. TEs were 4.9 and 5.9 ms, TR was 50 ms, and flip angle was 15°. Data were field-map corrected as described previously (Goense et al., 2008).

For anesthetized experiments a 12 cm custom-made quadrature RF coil was used that covered the entire brain. Images were acquired by using a four segment SE-EPI. The FOV was 8.0 × 7.2 cm^2, with a matrix size of 80 × 72, yielding a final resolution of 1.0 × 1.0 mm^2. The slices were acquired along the temporal lobe, and 22–25 slices with a thickness of 2 mm were typically needed to cover the entire brain. TE was 40 ms and TR was 2 s per segment, yielding a final temporal resolution of 8 s per volume. Data were acquired in a single session (experiment day) for each animal, which amounted to 1800 volumes for N08, 2160 volumes for C06, and 1368 volumes for L04. For anatomical reference a 16 segment SE-EPI was acquired in each scanning session. The matrix was 192 × 176 and the FOV was 8.0 × 7.2 cm^2 with 1 mm slice thickness. TE was 62 ms and TR was 3 s. Reference anatomical scans and the 3D FLASH for field mapping were acquired by using the same parameters as in awake experiments.

Data Analysis

EPI images were reconstructed by using Bruker ParaVision 4.0 software. Data were analyzed by using custom-written software in MATLAB (The MathWorks, Natick, MA, USA), SPM 2 and SPM 5 (Wellcome Department of Cognitive Neurology, London, UK [Friston et al., 1995]), and Caret 5.9 (Washington University, St. Louis, USA [Van Essen et al., 2001]). Data from awake monkeys were processed following the methods described in Goense et al., 2008. Images were realigned, field-map corrected, and coregistered with the anatomical image by using SPM 2. For anesthetized animals similar procedures were used. Images were smoothed by using a 3 mm (awake) or 2 mm (anesthetized) full width at half maximum Gaussian kernel. Statistical analysis was done in SPM 2 by using general linear model analysis with the default hemodynamic response function. Activation was thresholded (at a significance level of $p < 0.001$ uncorrected for multiple comparisons) and clustered in three dimensions by using a minimal cluster size of 5 contiguous voxels.

The high-resolution MDEFT anatomical image of each monkey was skull stripped by using MRIcro 1.39 (Chris Rorden, © 1999–2005) and imported into Caret 5.9. The segmentation, reconstruction, and inflation of cortex were done automatically with minimum manual correction (http://brainvis.wustl.edu/wiki/index.php/Main_Page). Functionally activated areas were assigned based on the atlas by Saleem and Logothetis (Saleem and Logothetis, 2006). For comparison with functional activation reported in the literature, images were referenced to the aforementioned atlas after normalization to the rhesus macaque template by McLaren et al. (McLaren et al., 2009) (http://www.brainmap.wisc.edu/monkey.html) by using the normalization routines in SPM5. All images are displayed referenced to the Frankfurt zero plane. AP positions refer to the AP positions for individual monkeys after normalization to the template. Locations of functional activation in the literature were estimated based on AP positions of individual animals when AP positions were given (typically not normalized to the macaque template); otherwise positions were estimated by comparing coronal slices shown in the figures to the atlas by Saleem and Logothetis (Saleem and Logothetis, 2006). In cases where activation extended over multiple slices, the average position was taken. Data from the left and right hemispheres were merged in the schematic figure (Figure 7).

SUPPLEMENTAL INFORMATION

Supplemental Information includes six figures and two tables and can be found with this article online at doi:10.1016/j.neuron.2011.02.048.

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