Cognitive Response Profile of the Human Fusiform Face Area as Determined by MEG

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Activation in or near the fusiform gyrus was estimated to faces and control stimuli. Activation peaked at 165 ms and was strongest to digitized photographs of human faces, regardless of whether they were presented in color or grayscale, suggesting that face- and color-specific areas are functionally separate. Schematic sketches evoked ~30% less activation than did face photographs. Scrambling the locations of facial features reduced the response by ~25% in either hemisphere, suggesting that configurational versus analytic processing is not lateralized at this latency. Animal faces evoked ~50% less activity, and common objects, animal bodies or sensory controls evoked ~80% less activity than human faces. The (small) responses evoked by meaningless control images were stronger when they included surfaces and shading, suggesting that the fusiform gyrus may use these features in constructing its face-specific response. Putative fusiform activation was not significantly related to stimulus repetition, gender or emotional expression. A midline occipital source significantly distinguished between faces and control images as early as 110 ms, but was more sensitive to sensory qualities. This source significantly distinguished happy and sad faces from those with neutral expressions. We conclude that the fusiform gyrus may selectively encode faces at 165 ms, transforming sensory input for further processing.

Introduction

The neural basis for our remarkable ability to identify and interpret faces is controversial. Are there 'centers' specific for processing faces? If so, does the specificity lie in perceptual-processing or in memory storage? If there are not truly specific face centers, then how do apparently face-specific deficits arise? Converging evidence suggests that an essential stage in the cerebral processing of faces occurs in the fusiform gyrus ~165 ms after stimulus onset. We report here data concerning the specificity of this response to human faces, as compared with animal faces, animals, objects,and sensory controls, and the generalizeability of this response to faces with different characteristics.

The first evidence implicating the fusiform gyrus in face processing was the observation that the basal occipitotemporal cortex is nearly always lesioned in patients with specific deficits in the recognition of familiar faces (prosopagnosia) (Meadows, 1974a; Damasio *et al.*, 1990; Sergent and Poncet, 1990; Sergent and Signoret, 1992). Similarly, studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have found that the fusiform gyrus is metabolically activated by faces (Haxby *et al.*, 1991; Sergent *et al.*, 1992, 1994; Puce *et al.*, 1995; Clark *et al.*, 1996; Kanwisher *et al.*, 1997; McCarthy *et al.*, 1997; Halgren *et al.*, 1999). Finally, intracranial EEG recordings have identified fusiform gyrus activity that is evoked selectively by faces at ~165 ms latency (Halgren *et al.*, 1991, 1994a; Allison *et al.*, 1994).

Although these multiple sources of evidence firmly establish that an important step in face processing occurs in the fusiform gyrus at ~165 ms, the exact nature of this processing remains in doubt. First, prosopagnosia is classically defined as a specific inability to recognize the faces of familiar people. However, some prosopagnosics also are deficient in judging the characteristics of unfamiliar faces, such as their age, gender and emotional expression (Bruyer, 1991). Many prosopagnosics may also show signs of amnesia, achromatopsia and/or visual agnosia (Farah, 1995), suggesting that the deficit may not be exclusive to faces. Finally, some prosopagnosics have difficulty in identifying particular exemplars of categories [e.g. a specific famous building (Damasio, 1989)], suggesting that their deficit may be in identifying particular individuals rather than faces *per se*.

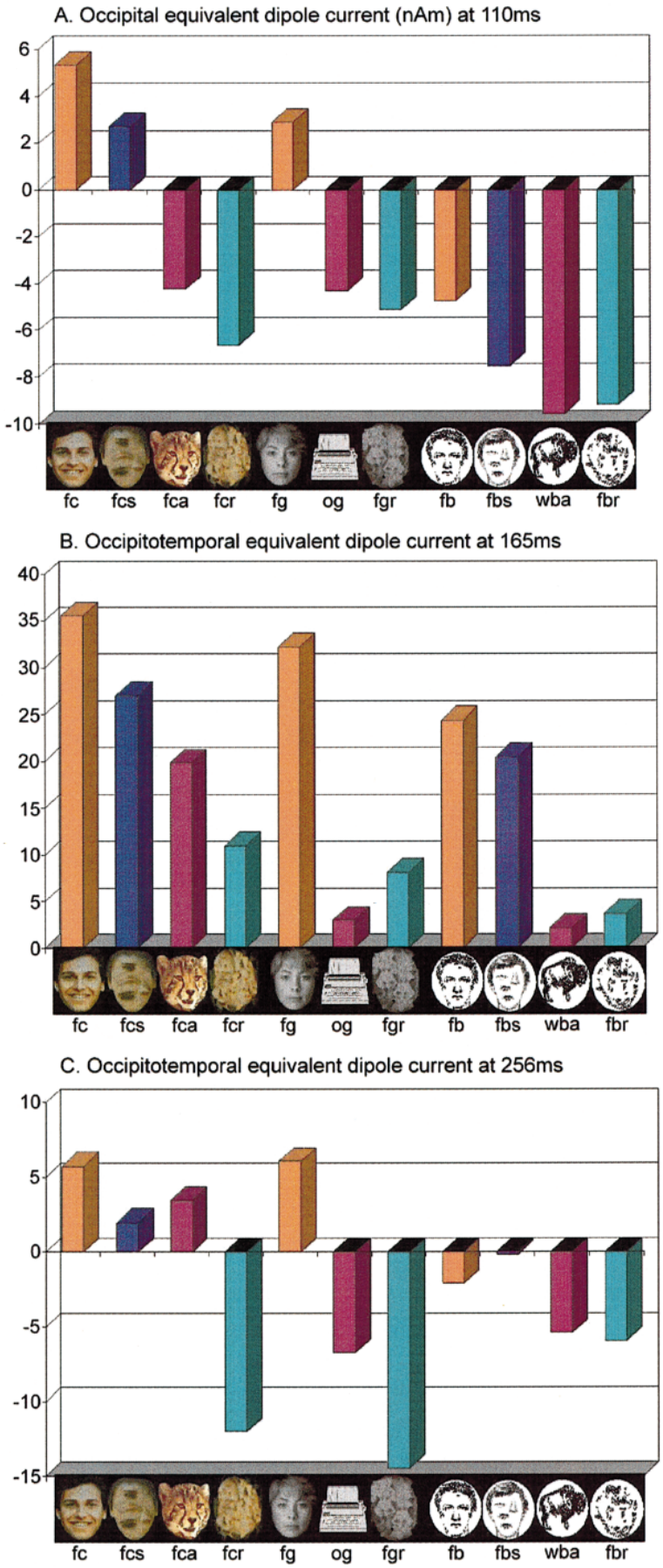
Which of these deficits are intrinsic and necessary parts of the prosopagnostic syndrome due to fusiform gyrus lesions, and which are incidental dissociable characteristics due to collateral damage of structures that happen to be adjacent or share a common blood supply is controversial (Damasio, 1989; Bruce and Humphreys, 1994; Farah, 1995). PET and fMRI studies cannot completely resolve these issues because they lack the temporal resolution necessary to isolate fusiform gyrus activity near 165 ms from that which occurs at longer latencies and appears to be under top-down influence from subsequent processing centers (Halgren *et al.*, 1994a; Marinkovic *et al.*, 1999).

In a preliminary study, Lu *et al.* recorded magnetic fields evoked by faces over the inferotemporal cortex (Lu *et al.*, 1991). In a more extensive recent report, Sams *et al.* fitted equivalent current dipoles (ECDs) to face-selective magnetic fields, and in one subject in whom the MRI was available, the ECD was located in the fusiform gyrus (Sams *et al.*, 1997). In the current study, three ECDs, localized to the left and right fusiform gyri and the ventral midline occipital region, were found to model the major features of the face-specific magnetic field. The fusiform ECDs had several characteristics resembling those previously found with direct intracranial recordings. These ECDs were used as spatial filters to characterize the fusiform response to faces and face-like stimuli. The fusiform response profile suggests that it performs very specific encoding of human faces at ~165 ms.

Materials and Methods

Informed consent was obtained from 10 normal subjects (8 male, 9 right-handed, aged 22–43 years). They were presented with 78 different visual stimuli in each of the following 11 categories (Fig. 1):

fc (face-color). Digitized color full-face photographs of human faces (1/2 male, 1/2 female; 1/3 happy [fc+], 1/3 neutral [fc±], 1/3 sad [fc–]; gender and expression were completely counterbalanced) from previously unfamiliar young European-origin adults, without facial hair, glasses, clothing or other verbalizable distinguishing features. Subjects posed in each photograph as happy, sad or neutral, according to instructions and after practice. Ratings of the facial expressions by 25 independent judges were highly consistent. Following digitization, the faces were processed so as to have the same color balance and size.


A. Occipital equivalent dipole current (nAm) at 110ms
6
4
2
0
-2
-4
-6
-8
-10
fc fcs fca fcr fg og fgr fb fbs wba fbr
B. Occipitotemporal equivalent dipole current at 165ms
40
35
30
25
20
15
10
5
0
fc fcs fca fcr fg og fgr fb fbs wba fbr
C. Occipitotemporal equivalent dipole current at 256ms
10
5
0
-5
-10
-15
fc fcs fca fcr fg og fgr fb fbs wba fbr

fg (face-grayscale). Photographs were obtained and digitized as for *fc*, and then were converted to grayscale (1/3 positive expression, 1/3 neutral, 1/3 negative; 1/2 male, 1/2 female).

fb (face-black and white). Black schematic faces on white backgrounds (1/2 male, 1/2 female, all neutral expression) were constructed using a forensic program (Mac-a-Mug Pro™) from hair (185 possibilities), eyes/eyebrows (118 possibilities), nose (66 possibilities), mouth (81 possibilities), chin/neck (46 possibilities) and ears (14 possibilities). After juxtaposing the features, the faces were individually edited for realism. Stimuli were full-face European-origin adults, without verbalizable distinguishing features.

fcs (face-color-scrambled). Photographs of faces obtained and treated in the same manner as *fc* (except that they were of different people), but with the features (eyes/eyebrows, nose, and mouth) moved to different unnatural positions in the face.

fbs (face-black and white-scrambled). Similar to *fb* but with the features moved to unnatural positions.

fcr (face-color-randomized). The *fc* stimuli were distorted so that they were not recognizable as being faces. These stimuli had the same size, form and location in the visual field as the original stimulus, and approximately the same colors and intensity.

fgr (face-grayscale-randomized). Same as *fcr* but grayscale.

fbr (face-black and white-randomized). Same as *fb* but distorted beyond recognition as a face.

fca (face-color-animal). Digitized color photographs of the faces of many different mammalian species. These stimuli were approximately the same size as the human faces but were less consistent in outline.

wba (wholebody-black and white-animal). Black and white sketches of the entire bodies of different species, mostly mammalian but also a few reptiles, birds and insects.

og (objects-grayscale). Photographs and drawings of common inanimate (n = 72; houses, airplanes, scissors, clocks, books, etc.) and natural (n = 6; flowers, shell, tree, apple) objects.

Stimulus duration was 240 ms, and interstimulus interval (onset-to-onset) was either 1530 ms (subjects 1–7) or 1050 ms. A given person was photographed or sketched only once. The fixation point for all face stimuli fell between and slightly below the eyes. Color and grayscale stimuli were presented directly on a black background. Black and white stimuli were presented on an oval white background that was again surrounded by black. The stimuli were projected into the magnetically shielded room through an aperture in the chamber, and subtended a visual angle of 10.5° vertical × 7.5° horizontal. The measured rise time (from the first pixel of a picture to the last one) was 7 ms, and the latency jitter of the trigger pulse with respect to stimulus onset was ±7 ms. Stimulus presentation and task control were performed by MacProbe™ (Hunt, 1994). The measurement room was dark for five subjects (nos. 3–7), and dimly lit for the others. Stimuli were presented in 13 blocks of 72 stimuli each – including six repetitions of an immediately preceding stimulus. Stimuli of different categories were arranged in random order. The subjects were instructed to lift the index finger (right or left hand on alternate blocks) every time they saw the same picture twice in a row. MEG signals were recorded with a passband of 0.03–90 Hz using a 122-channel Neuromag-122TM planar dc-SQUID magnetometer covering the entire scalp (Hämäläinen *et al.*, 1993). The signals were digitized at 297 Hz and averaged on-line. Vertical EOG (0.3–100 Hz) and EEG (0.01–100 Hz) from Fz, Cz, Pz, T5 and T6 of the international 10–20 system, referred to the nose, were measured simultaneously. For technical reasons, no EEG data were collected from subject 10. Epochs were discarded from analysis whenever the amplitude of the EOG or EEG exceeded 150 µV, or any of the MEG signals exceeded 3000 fT/cm.

Seven subjects were measured twice. Since the MEG responses from the two task replications were highly similar, they were averaged together, resulting in ~132–156 single trials for each category. The locations, orientations and strengths of the ECDs were found with a least-squares fit in a spherical volume conductor, the center of which was equal to the local center of curvature of the surface of the brain in the occipito-parietal area, determined on the individual MRIs (Hämäläinen *et al.*, 1993). Since no differences were observed between responses to colored versus grayscale stimuli, these responses were combined separately for faces and randomized faces for source modeling and display in Figures 2–6. ANOVA was used for statistical comparisons (Woodward *et al.*, 1990). Where appropriate, Tukey or Bonferroni corrections were made to adjust significance levels for the effects of multiple comparisons, and all ANOVAs involving more than two factors have been corrected for sphericity. All reported results were significant at P <0.05.

Results

Source Modeling

MEG signals with multiple peaks and a complex topography were evoked by both faces and randomized faces (Fig. 2). Face-selective responses (calculated by subtracting the responses to randomized faces from those evoked by normal faces) appeared to begin ~90 ms and continue for at least 200 ms (Fig. 2). These subtraction waveforms were characterized by an early midline occipital (MO) peak followed by right and left occipitotemporal (ROT and LOT) responses. Little or no activity was detected over frontal, parietal and central sites. The MEG and EEG waveforms demonstrated a remarkable level of consistency across subjects, especially in the subtraction waveforms (Fig. 3).

The MO response reached peak amplitude at 118–147 ms post stimulus onset, at a latency of 127 ± 12 ms (mean ± SD; Fig. 3, top row). In most subjects, this activity was stronger to the randomized faces. Consequently, the polarity of this response inverted in the subtraction waveforms, because randomized faces were in the subtrahend (Figs 3, 4). In contrast, the ROT response was clearly larger to faces than to randomized faces between 150 and 185 ms. MEG responses from the typically most active ROT sensor appeared considerably more regular across individual subjects than did the responses from the corresponding LOT sensor (Fig. 3). In addition, a second peak was apparent in the ROT subtraction waveforms which was not apparent in most LOT MEG responses.

Despite the greatly simplified MEG patterns produced by subtracting randomized faces from faces, it was still necessary to use three dipoles to model the activity during the first 270 ms (Figs 4, 5): MO-ECD at the inferior occipital midline, and LOT-ECD and ROT-ECD at the left and right basal temporo-occipital junctions. The signals were strong and the field patterns stable. Thus the ECD locations and directions were not markedly affected by moderate changes in the channel selections and times used for ECD fitting. Source modeling was facilitated by choosing times and sites which appeared to have activity principally from a single source, rather than at the time of

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Figure 1. Cognitive profiles of the occipital dipole at 110 ms (*A*), and the occipitotemporal dipole at 165 (*B*) and 256 ms (*C*). The first four bars are responses to color face photographs and controls, the next three to grayscale face photographs and controls, and the last four to black and white face sketches and controls. Strong differentiation in the responses of faces and nonfaces is seen for all three dipoles, and for all three types of sensory presentation. For OT165 (*B*), faces (orange bars: fc, fg, fb) evoke substantially more activity than the randomized faces (light blue bars: fcr, fgr, fbr), regardless of sensory quality. Objects (og) and whole animal bodies (wba) evoke very little activity. Scrambled human faces (dark blue bars: fcs or fbs) and normal animal faces (fca) evoke intermediate levels. Note that the polarity of the MO110 response has been inverted to facilitate comparison with OT165.

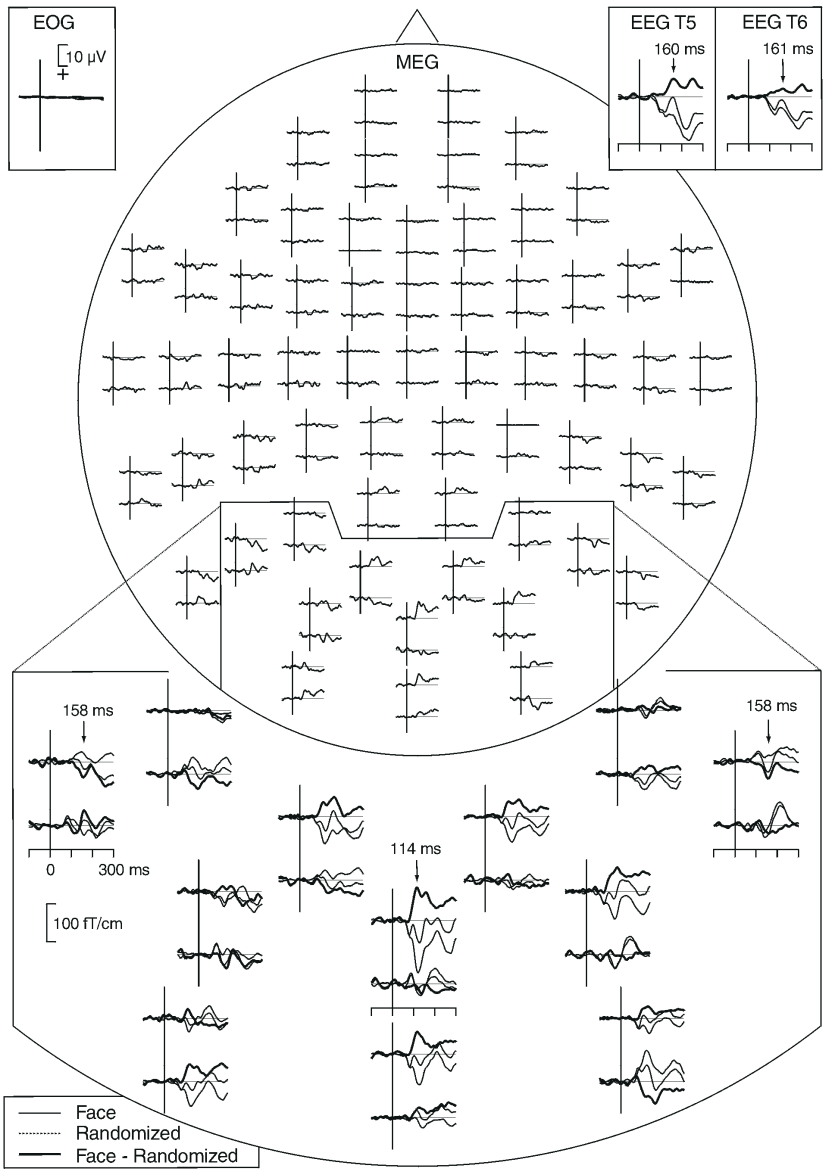

Figure 2. Face-selective MEG and EEG waveforms from subject 2. Magnetic fields were recorded in two orthogonal directions at 61 locations; front of the head is at the top of the figure; right is right. The analysis period is from 100 ms before to 300 ms after stimulus onset. EEG is shown from occipitotemporal areas (T5 left, T6 right); EOG was recorded above and below the eyes. The posterior MEG channels are enlarged, and the waveforms evoked by faces, randomized faces, and their subtraction (i.e. faces minus randomized faces), are shown. In other channels, only the subtraction waveforms are shown. The averaged responses have been low-pass filtered at 40 Hz.

maximal activity. Specifically, the MO-ECD was found on occipital sites at a latency of 129 ± 15 ms (range: 118–160), the ROT-ECD at 187 ± 42 ms (range: 155–277) and the LOT-ECD at 168 ± 23 ms (range: 155–218). All ECDs were approximately vertical (Fig. 5). The selection of latencies and sites for dipole modeling was validated *post hoc* by goodness-of-fit criteria. For the MO-ECD, the goodness-of-fit (i.e. the percentage of variance explained, *g*) was 91 ± 6%, and exceeded 85% in 9/10 subjects. The radius of the 95% confidence volume was 4.2 ± 2.6 mm. For the ROT-ECD (in 9 subjects), *g* was 88 ± 7%. The radius of the 95% confidence volume was 4.1 ± 1.6 mm. For the LOT-ECD (7 subjects), *g* was 91 ± 5%, and the radius of the 95% confidence volume was 6.4 ± 4.1 mm.

The principal analyses of the cognitive profile of the MO-ECD were performed at 110 ms (termed MO110) because at this latency the OT-ECDs were not yet active and so did not contaminate the MO-ECD measures. In order to retain all 10 subjects for analysis of the occipito-temporal response, the main analyses were performed using the right OT-ECD when possible and the left OT-ECD in the one subject who did not show a right OT-ECD. Measurements were made of the OT-ECD strength curves at two peaks with latencies of 165 ± 9 ms (range: 146–183; termed OT165), and 256 ± 17 ms (range: 237–289; termed OT256).

ECD Locations and Time-courses

MR images were available for all subjects. The translation between the MR and MEG coordinate systems was made using small coils placed on the scalp and fiducial landmarks as described by Hämäläinen (Hämäläinen *et al.*, 1993). In all 10 subjects the MO-ECD was located in the posterior inferior midline occipital lobe, in or inferior to primary visual cortex

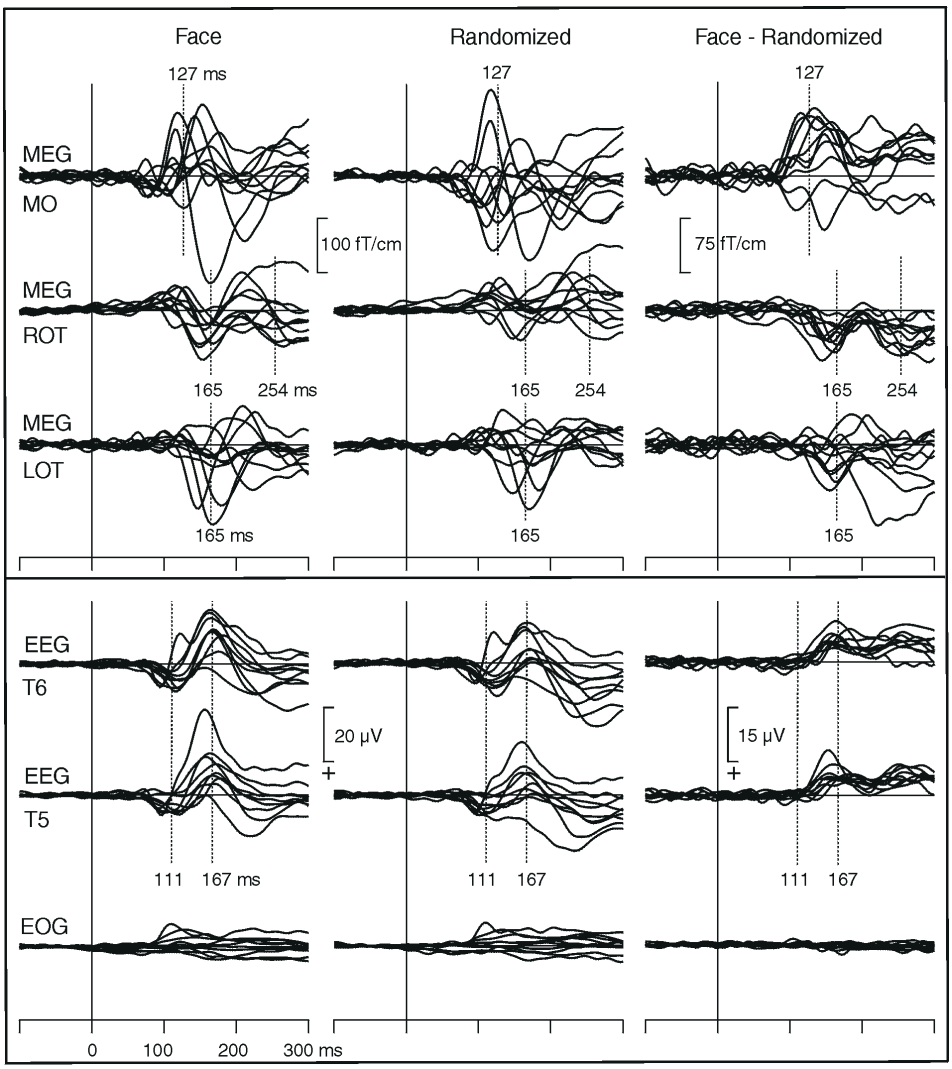

Figure 3. MEG, EEG and EOG waveforms from 100 ms before to 300 ms after stimulus onset recorded by the same sensors (indicated by arrows in Fig. 2) across all 10 subjects. The left column shows activity evoked by faces, center by randomized faces, and right by the difference (i.e. face-selective activity). The MO (midline occipital MEG) activity is generally larger to randomized faces than to faces, whereas the ROT (right occipitotemporal MEG) traces are clearly larger to faces. In comparison with ROT, the LOT (left occipitotemporal MEG) responses are less regular, and only show one discernible peak in the subtraction waveforms (average latency of 165 ms), whereas the ROT waveforms clearly show two successive peaks at 165 and 254 ms. A bilateral face-selective occipitotemporal EEG response is seen at an average latency of 167 ms (T5 left; T6 right). The vertical lines indicate the approximate average latencies used for measuring cognitive profiles. Low-pass filtering at 40 Hz.

(Figs 4, 5). In 9 subjects (except subject 8) it was possible to localize a vertically oriented ROT-ECD in the inferior surface of the posterior fusiform gyrus (5 subjects), or in the fundus of the occipitotemporal sulcus between the fusiform and inferior temporal gyri (4 subjects). An LOT-ECD could be localized in 7 subjects (except subjects 5, 7, 9), and it was most often situated in the fusiform gyrus (5 subjects) or the sulcus lateral to it (1 subject). The ROT-ECD and the LOT-ECD were located and oriented symmetrically across the midline (Fig. 6).

The three-dipole model was used for modeling the original, unsubtracted responses: while keeping the location and direction of each ECD constant, dipole magnitudes were allowed to vary as a function of time, thus producing the best match to the observed field patterns in the 'least-mean-squares' sense. Since all of the modeled sources were at the back of the head, only the 96 most posterior MEG channels were considered for these calculations. The ROT-ECD strength curves tended to be triphasic, with small peaks at ~130 and ~250 ms surrounding the prominent sharp peak at ~165 ms (Fig. 5). This pattern was less commonly observed in the LOT-ECD strength curves. The most consistent feature in the MO-ECD strength curves was a monophasic deflection from about 100 to 160 ms (Fig. 5). This deflection was strongest to *randomized* faces, whether derived from color photographs, grayscale photographs or from black and white line drawings (Fig. 7). In contrast, no consistent activation was discernable in the same latency range to actual faces, whether color, grayscale or black and white.

EEG Responses

The strongest EEG responses were evoked by faces and randomized faces at the T5 and T6 electrodes, placed over the left and right occipitotemporal cortices (Fig. 2). Two main peaks were seen on these channels (Fig. 3): a scalp-positive peak (P111) measured as the maximum potential between 94 and 127 ms (average 111), and a negative peak (N167) measured as the minimum potential between 152 and 182 ms (average 167). P111 was marginally earlier to faces than to randomized faces (F = 9.31; df 1,8; P < 0.02; a 2 ms difference), but its peak

Figure 4. Isofield contour maps (50 fT step/line) of subject 3 to faces and randomized faces, and the map resulting when the signals evoked by randomized faces is subtracted from that evoked by faces. The sensor array is viewed from the back at 120 ms after stimulus onset. Due to their similarity, the superior occipital field patterns to faces and randomized faces are eliminated in the subtraction. In contrast, the inferior occipital patterns to faces *are* different from those to randomized faces, resulting in a dipolar pattern in the subtraction. Subject 3.

amplitude was not different. In contrast, the peak amplitude of N167 was greater to faces than to randomized faces (Fig. 3; $F = 141.93$; *df* 1,8; $P < 0.0001$), but its latency was not different. P111 was significantly larger over the right hemisphere ($F = 18.24$; *df* 1,8; $P < 0.005$), but N167 was not lateralized.

Effects of Faceness, Feature Position and Sensory Quality (Fig. 1)

Separate ANOVAs were performed on the MO110, OT165 and OT256 ECDs, with Faceness (normal, randomized) and Sensory Quality factors (color, grayscale, black and white). The Faceness × Sensory Quality interaction was significant for MO110 and OT256 [$F(2,18) > 16.1$, $P < 0.0002$] but not for OT165. For MO110 and OT256, this reflected a greater effect of Faceness for photographs than for sketches. The Faceness main effect was very strong for all sources [$F(1,9) > 10.2$, $P < 0.01$]. Simple comparisons between normal and randomized faces were significant for all three ECDs when considering separately the color, grayscale and black and white stimuli [$F(1,9) > 10.1$, $P < 0.05$], except that (after Tukey correction) the MO110 and OT256 strengths were not significantly different for black and white normal versus randomized faces. The time-course of the MO source was examined with separate ANOVAs at fixed latencies of 80, 90, 100, 110 and 120 ms, as well as the average peak latency of 127 ms. Significant effects were observed at 110 ms ($F = 10.2$, $P < 0.01$), 120 ms ($F = 16.2$, $P < 0.003$) and 127 ms ($F = 24.0$, $P < 0.0009$), but not earlier at 80 or 90 ms. A trend was present at 100 ms [$F(1,9) = 4.6$, $P < 0.06$]. The Sensory Quality main effect was significant for MO110 and OT165 [$F(2,18) > 6.4$, $P < 0.02$], but not for OT256. The effect of Sensory Quality was especially strong for MO110, where simple comparisons demonstrated significant differences between the face photographs (either color or grayscale) and the black and white face sketches [$F(1,9) > 11.7$, $P < 0.05$]. For OT165, randomized color controls evoked >2.5 times more activation than did randomized black and white controls. This, however, was not significant after Tukey correction. In no case was any significant difference observed between color and grayscale faces. Thus, all three dipoles strongly distinguished faces from randomized faces, especially for photographs. Sensory characteristics had an independent influence on the earlier responses.

As in the analyses just described, separate ANOVAs were performed on the MO110, OT165 and OT256 ECDs, with Faceness and Sensory Quality factors. However, in this case, the Faceness factor included scrambled faces as well as normal and randomized faces as levels, and the Sensory Quality factor included only color and blackand white faces as levels. The main effects and interactions of these analyses basically replicated the preceding analyses, but additional comparisons were possible regarding the effects of proper feature arrangement. Again, the Faceness × Sensory Quality interaction was significant for MO110 and OT256 [$F(2,18) > 15.0$, $P < 0.0005$] but not OT165, the Faceness main effect was highly significant for all dipoles, and the Sensory Quality main effect was significant for MO110 and OT165 but not OT256. With one exception (across all latencies and locations, both color and black and white) ECD strengths for scrambled faces were intermediate between their strengths for faces and randomized faces. After Tukey correction, the MO110 and OT165 responses were significantly different to scrambled face photographs as opposed to faces [$F(1,9) > 8.2$, $P < 0.05$]. In summary, scrambled faces evoked a level of activity that was intermediate between that evoked by normal faces and that evoked by controls (randomized faces). This effect was true for color digitized faces as well as black and white sketches.

Specificity for Human Faces versus Animal Faces, Objects and Whole Animal Bodies

Separate ANOVAs were performed for the MO110, OT165 and OT256 ECDs, including normal digitized color human and animal faces, and the corresponding randomized face controls. Animal faces evoked a level of activity in all ECDs and latencies that was intermediate between that evoked by human faces and that evoked by randomized controls. Significant main effects were observed for all ECDs [$F(2,18) > 15.0$, $P < 0.001$]. Tukey-corrected simple comparisons showed that the difference between human and animal faces was significant for MO110 and for OT165 [$F(1,9) > 14.7$, $P < 0.01$], but not for OT256. In contrast, the difference between animal faces and sensory controls was significant for OT165 and OT256 [$F(1,9) > 7.8$, $P < 0.05$], but not for MO110.

Separate ANOVAs were performed for the MO110, OT165 and OT256 ECDs, including normal digitized grayscale human faces, grayscale images of objects and the corresponding randomized grayscale controls. Main effects were observed for all ECDs [$F(2,18) > 8.6$, $P < 0.003$]. Tukey-corrected simple comparisons showed that for all latencies and ECDs, the difference between faces and objects was significant [$F(1,9) > 11.0$, $P < 0.05$]. In contrast, the difference between objects and controls was never significant (although a trend was present for OT256).

Separate ANOVAs were performed for the MO110, OT165 and OT256 ECDs, including black and white sketches of faces or of

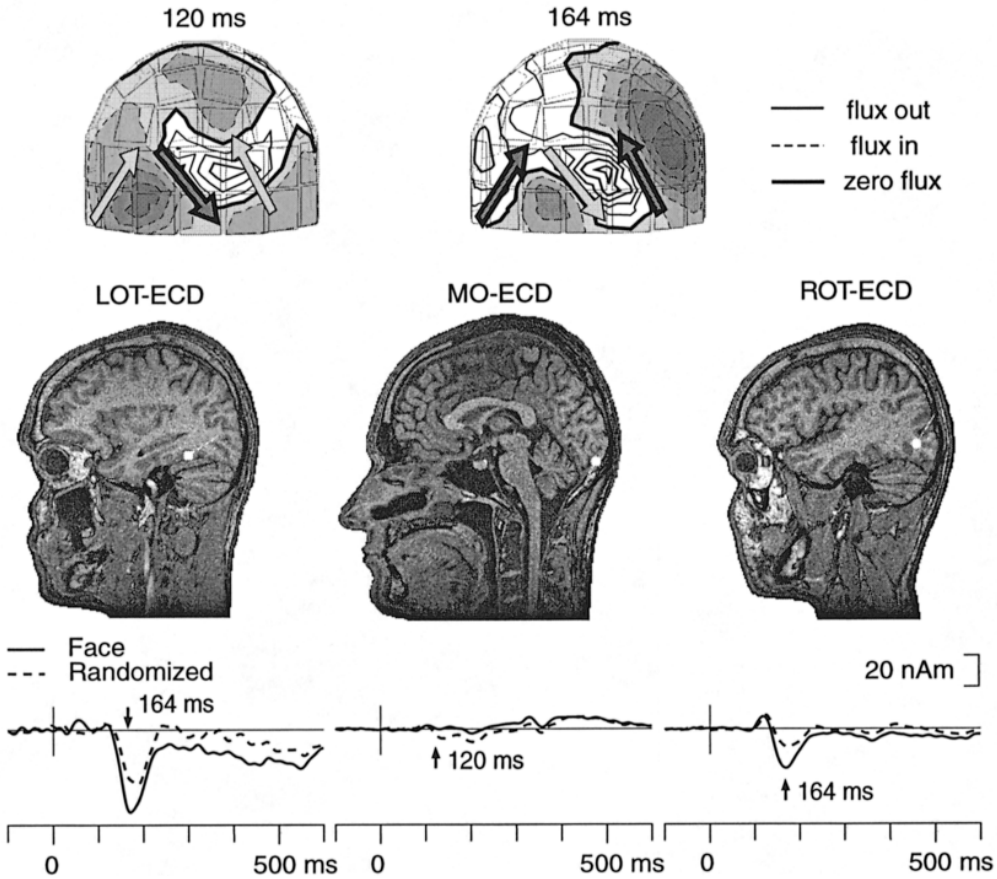

Figure 5. MEG responses at 120 and 165 ms after face onset in subject 4. In the top row are shown the isofield contours at the back of the head evoked by faces (normal minus randomized) at 120 ms (left plot, 30 fT/line) and 165 ms after face onset (right plot, 50 fT/line). The ECDs used to model the fields are shown as arrows superimposed on the contours (as projected to the surface). The MO field pattern (modeled by the center arrow) is dominant at the earlier latency, whereas the LOT (left arrow) and ROT (right arrow) fields predominate later. In the middle row, the same ECDs are superimposed on subject 4's MRI. The LOT-ECD is located to the fusiform gyrus, and the ROT-ECD is located more posterolaterally in the sulcus separating the fusiform and inferior temporal gyri. The estimated time-courses of the ECDs are shown below. The MO-ECD is *smaller* to faces than to randomized faces from ~110 ms (center), whereas the LOT and ROT-ECDs are *larger* to faces from ~140 ms, and have a clear peak at 165 ms. Note that although the MO signals were stronger at the sensors than the ROT or LOT signals (Figs 2 and 3), the corresponding dipole was weaker since it was located closer to the surface. Dipole arrow sizes on the field contours are not comparable.

whole animal bodies, and the corresponding randomized black and white controls. A significant effect of category was found for OT165 [$F(2,18) = 26.9$, $P < 0.0001$], but not other ECDs. Simple comparisons showed significant differences between whole animals and faces in OT165 [$F(1,9) = 35.2$, Tukey-corrected $P < 0.001$], and trends were found in the other ECDs and latencies. No significant differences were found between the responses to animals and controls. In summary, animal faces activated the OT165, but at a level which was below its activation by human faces. Neither objects nor animal bodies significantly activated the face-specific ECDs.

Sensitivity to Human Face Emotional Expression, Gender and Repetition

ANOVAs with a single factor of Emotion (positive, negative or neutral expression), were performed using data combined from color and grayscale photographs. A significant main effect of Emotion was found for the MO110 [$F(2,18) = 10.6$, $P < 0.001$], but not for OT165 or OT256. In order to explore the time-course of this effect, additional ANOVAs were performed on the MO-ECD at other latencies. The main effect of Emotion was also significant at 100 and 120 ms [$F(2,18) > 5.0$, $P < 0.02$] but not at 127 ms. Simple comparisons showed that at 100 and 110 ms, positive expressions were different from controls [$F(1,9) > 11.4$, $P < 0.05$, corrected using Tukey], whereas only at the 110 ms, were negative expressions significantly different from positive [$F(1,9) = 12.4$, $P < 0.05$]. No significant effects of Gender (male or female, using data from black and white faces only) were seen for any ECD.

All of the analyses described above were performed on the activation evoked by non-target stimuli (i.e. to the first appearance of a given stimulus within a task). In contrast, the effects of repetition were evaluated by comparing the activations to all non-target (i.e. novel) stimuli combined versus all target (i.e. repeated) stimuli combined. No significant differences or even trends were seen for any of the ECDs or latencies [all $F(1,9) < 0.9$].

Lateralization of Occipitotemporal Activation

LOT- and ROT-ECD strengths were compared in the six subjects showing bilateral responses. Measures were made at the peak latencies of 165 ± 10 ms (range: 157–183) for ROT, and 167 ± 24 ms (range: 151–216) for LOT. The ANOVA had two factors: Category (including all 11 stimulus categories) and Side (ROT or

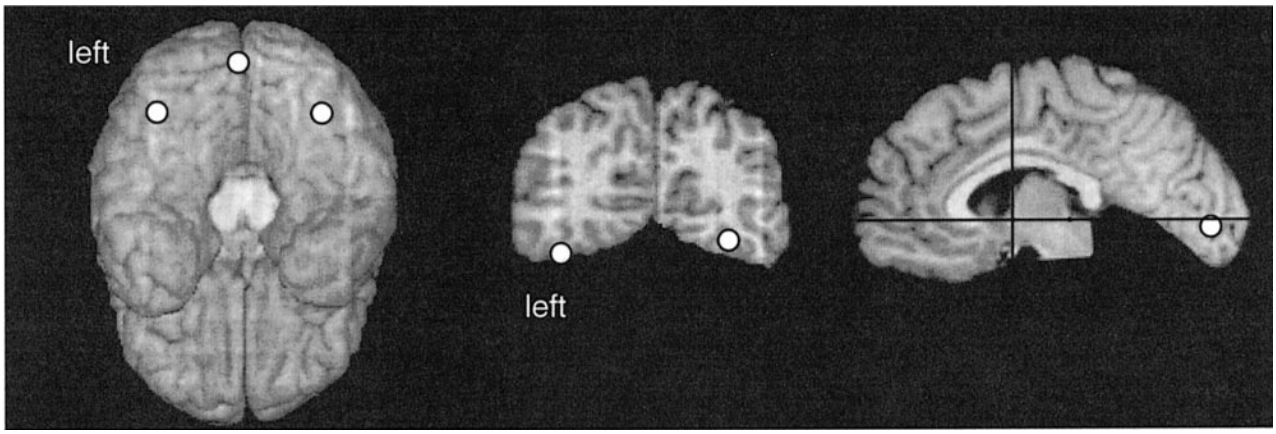

Figure 6. Average locations across subjects for the MO-, ROT- and LOT-ECDs. (Left) Sources projected on a view of the cerebrum from below (left on left, occipital pole up). The cerebellum has been removed from this MRI surface reconstruction. (Middle) ROT and LOT source locations shown on a coronal MRI slice 65 mm posterior to the anterior commissure. (Right) MO source location on a midsagittal slice. The white vertical line indicates the location of the coronal slice, while the black lines show the Talairach coordinate system axes. After normalization of the brains (Talairach and Tournoux, 1988), the MO sources ($n = 10$) were located at the Talairach coordinates: –2 ± 6, –86 ± 6, –3 ± 12 (mean ± SD, distance in mm to the right of midline, anterior to the anterior commissure, and above the anterior commissure–posterior commissure plane). Similarly, the Talairach coordinates of the ROT sources ($n = 9$) were +35 ± 8, –64 ± 10, –8 ± 5, and those of the LOT sources ($n = 7$) were –38 ± 7, –65 ± 12, –14 ± 7.

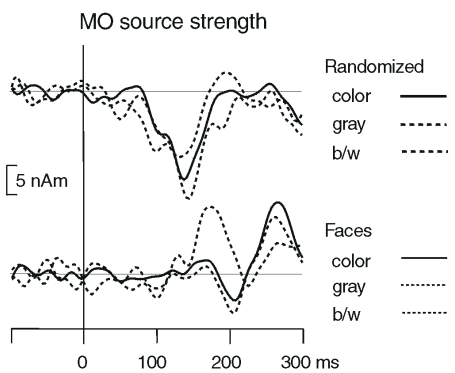

Figure 7. The strength of the MO dipole of subject 10 as a function of time for six stimulus conditions. Note that from about 100 to 150 ms after stimulus onset, this area appears to be activated only by randomized faces, and not by faces, regardless of whether the original face stimuli were color or grayscale digitized photographs, or were black and white line drawings.

LOT). The Category main effect was significant [$F(10,50) = 16.3$, $P < 0.0001$], but the Side main effect was not [$F(1,5) = 0.5$], nor was their interaction [$F(10,50) = 1.2$]. The statistical power of these comparisons was low. However, examination of the marginals showed that in all cases the ROT measure was larger than the LOT, and that this difference was most pronounced, in absolute terms, for the normal faces (a difference of 13.0 nAm for color faces, 12.1 nAm for grayscale, and 6.7 nAm for black andwhite). In contrast, this difference was smallest for nonface items, such as objects (–0.7 nAm) and animal bodies (1.0 nAm). When considering only the four subjects with the clearest bilateral OT-ECD, the ROT-ECD was about three times stronger than LOT-ECD.

It has been proposed that the right hemisphere is more sensitive than the left to the spatial configuration of facial features. This sensitivity would be expected to result in an enhanced sensitivity of the ROT-ECD response to scrambling the location of facial features. Therefore a separate ANOVA was performed with three factors: Sensory Quality (color, black and white); Faceness (normal, scrambled, randomized); and Side (LOT, ROT). The three-way interaction was not significant [$F(2,10) = 0.8$], nor were the Faceness × Side [$F(2,10) = 1.4$], or Sensory Quality × Side [$F(1,5) = 0.9$] interactions. As expected, the Sensory Quality × Faceness interaction was significant, as were the main effects of Sensory Quality and Faceness. However, the main effect of Side was not [$F(1,5) = 0.6$]. Despite the lack of significant main effects or interactions involving Side, the data were subjected to further analyses to search for any indication that the ROT-ECD is more sensitive to spatial configuration than the LOT. In Tukey corrected simple comparisons, ROT strength was significantly different to scrambled versus randomized faces [$F(1,5) = 17.9$, $P < 0.01$], whereas only a trend toward a difference was observed between normal versus scrambled faces [$F(1,5) = 3.9$]. In contrast, LOT strength was significantly different to normal versus scrambled faces ($F[1,5] = 19.2$, $P < 0.05$), as well as between scrambled versus randomized faces [$F(1,5) = 18.7$, $P < 0.05$]. Thus, the trend in the current data is for greater sensitivity to the spatial arrangement of facial features in the *left* hemisphere.

unclear if lateralized!!! not clear-cut results

Discussion

Validation of the OT-ECD by Comparison with fMRI, PET and Intracranial EEG

The localization of generating structures given extracranial MEG data (i.e. the inverse problem) is indeterminate, and sources with the apparent depth and extension of the fusiform face area can pose particular problems for accurate localization (Hari *et al.*, 1988; Hämäläinen *et al.*, 1993). Thus, it is important to validate the location of the OT-ECD against techniques that are not susceptible to these limitations. The posterolateral fusiform location of the OT-ECD corresponds well to that found using PET (Sergent *et al.*, 1992; Haxby *et al.*, 1991) and fMRI (Puce *et al.*, 1995; Clark *et al.*, 1996; Kanwisher *et al.*, 1997; McCarthy *et al.*, 1997; Halgren *et al.*, 1999). In our subject 9, this fMRI/MEG correspondence was confirmed within-subject using identical face and control stimuli (Halgren *et al.*, 1999). For example, the Talairach coordinates of the response maximum in a number of previous studies (Haxby *et al.*, 1991; Clark *et al.*, 1996; Kanwisher *et al.*, 1997; Halgren *et al.*, 1999) were 38, –60, –7, as compared to the average location of the ROT-ECD at 35, –64, –8. This close correspondence suggests that the OT-ECD is indeed

measuring activity in the fusiform face area rather than in a second, more diffuse and less selective locus of activation to faces in ventrolateral occipitotemporal cortex that has also been described with fMRI (Malach *et al.*, 1995; Halgren *et al.*, 1999). The OT-ECD is far inferior and posterior to a third face-selective area seen with fMRI in the region of the superior temporal sulcus (Puce *et al.*, 1995, 1996, 1998; Halgren *et al.*, 1999).

The anatomical location and peak latency of the OT-ECDs correspond very well to those recorded from the fusiform gyrus using subdural (Allison *et al.*, 1994) or depth electrodes (Halgren *et al.*, 1991, 1994a) – the latter studies used the same stimuli as the current study. The depth potential to faces at ~165 ms is negative when measured by subdural electrodes passing underneath the fusiform gyrus (Allison *et al.*, 1994), and is usually positive when measured by depth electrodes passing in the white matter of the fusiform gyrus, above its inferior surface (Halgren *et al.*, 1994a). This implies that the generator on the inferior fusiform gyrus surface can be modeled as a vertically oriented dipole, with the intracellular current pointing upwards, and thus generating a magnetic field with the same general polarity and orientation as was observed in the current study. Finally, the OT-ECD to faces resembles the directly recorded fusiform EEG in being composed of multiple components, with peaks of alternating polarity at latencies of about 130, 165 and 240 ms (Halgren *et al.*, 1994a).

The face-selective EEG response recorded in this study at 167 ms appears to correspond to that previously reported (Seeck and Grüsser, 1992; Jeffreys *et al.*, 1992), as does its scalp distribution (Smith and Halgren, 1987; Bentin *et al.*, 1996; Marinkovic and Halgren, 1999). The nearly identical peak latencies of N167 and the OT-ECDs would seem to support a fusiform gyrus generation of the EEG response as well as the MEG. However, fMRI and depth recordings have identified face-selective activity in the posterior middle temporal gyrus that could also contribute to the scalp EEG response to faces (Halgren *et al.*, 1994a, 1999; Puce *et al.*, 1995, 1996, 1998).

Location and Laterality of the OT-ECD with Respect to the Lesion Causing Prosopagnosia

The current finding that a strong response selective for unfamiliar faces occurs in the same area where lesions cause prosopagnosia (Meadows, 1974a; Damasio *et al.*, 1990; Sergent and Poncet, 1990; Farah, 1995), provides additional support for the position that prosopagnosia reflects a general deficit in processing faces, rather than a deficit confined to the recognition of familiar faces (Farah, 1995). This is consistent with PET/fMRI studies, where the fusiform gyrus has been found to be activated both in tasks involving familiar faces (Sergent *et al.*, 1992), and those involving unfamiliar faces (Haxby *et al.*, 1991; Clark *et al.*, 1996; Kanwisher *et al.*, 1997; McCarthy *et al.*, 1997; Halgren *et al.*, 1999). The specific deficit in some cases of prosopagnosia for familiar faces may reflect damage that includes the anteromedial temporal lobe as well as the fusiform gyrus (Damasio *et al.*, 1990).

It is unclear whether bilateral lesions are necessary for prosopagnosia (Meadows, 1974a; Damasio *et al.*, 1990; Sergent and Poncet, 1990; Farah, 1995), or whether unilateral right lesions can be sufficient (Landis *et al.*, 1986; Benton, 1990; De Renzi *et al.*, 1996). The current data, in agreement with previous MEG studies (Sams *et al.*, 1997), suggest that there is an overall right > left laterality in fusiform face-selective activity, but that there is also a high level of individual variability. Partial dominance has also been reported in split-brain patients in whom both disconnected hemispheres can recognize faces, but the right hemisphere is more efficient at face processing (Levy *et al.*, 1972; Sergent, 1990). Similarly, PET and fMRI activations range from highly right-lateralized (Sergent *et al.*, 1992, 1994; McCarthy *et al.*, 1997), or partially right-lateralized (Haxby *et al.*, 1991; Clark *et al.*, 1996; Kanwisher *et al.*, 1997), to roughly bilateral (Puce *et al.*, 1995; Halgren *et al.*, 1999). Assuming that the ROT and LOT-ECD identify areas capable of supporting face encoding, our data suggests that in most people (7/10 in our small group), bilateral lesions would be necessary to cause prosopagnosia, but that in a minority (2/10), unilateral right lesions would be sufficient. Prosopagnosia has not been reported after unilateral left lesions. However, our finding of one subject with only LOT-ECD suggests that this may also be possible.

Selectivity of the OT165 for Human Faces

The selectivity of the OT165 for human as opposed to animal faces or bodies is consistent with other fMRI (Kanwisher *et al.*, 1999), as well as neuropsychological evidence (Bruyer, 1991; McNeil and Warrington, 1993). Similarly, the very small OT165 response to objects as compared to faces would seem to correspond very well with the basic finding of prosopagnosia: lesions can produce deficits in identification of faces with preserved identification of objects (De Renzi, 1989; Sergent and Signoret, 1992), as well as previous findings with fMRI (Kanwisher *et al.*, 1997). The current results demonstrate that this face-specificity in the fusiform gyrus is present at an early latency. This in turn suggests that fusiform gyrus lesions could cause prosopagnosia through specifically impairing face-encoding, rather than a general degradation in visual encoding. Note that the current results do not rule out the possibility that post-perceptual processes necessary for individual identification across all categories of visual stimuli are impaired in some prosopagnosics (Damasio, 1989).

Scrambling the locations of facial features (eyes, mouth and nose) reduced the OT165 response by ~25% for both photographed and drawn faces. This reduced response is consistent with the great behavioral sensitivity that normal subjects show toward the spatial arrangement of facial features (Bruce and Humphreys, 1994). Indeed, Farah has proposed that prosopagnosias may result from a deficit in the simultaneous configurational analysis of complex visual stimuli (Farah, 1995). The current finding of a much stronger OT165 activation by faces with scrambled features than by well-formed objects or animal bodies is not consistent with these proposals. Rather it suggests that even though fusiform gyrus processing *is* sensitive to the spatial distribution of facial features, its *primary* specificity is for human faces.

On the basis of studies in split-brain subjects (Levy *et al.*, 1972), the hypothesis has been advanced that the right hemisphere processes faces in a 'gestalt' or 'holistic' manner, being especially sensitive to the configuration of facial features, and that the left hemisphere processes faces in an 'analytical' or 'piecemeal' manner, being sensitive to the categories of particular features. No evidence for this hypothesis was found in the current study: the activation to scrambled faces was reduced on both sides by ~25% as compared to normal faces.

Generalization of the OT165 across Different Categories of Faces

The OT165 response not only was selective for human faces as compared to animals and objects, but also generalized to human faces with very different sensory characteristics. First, the

OT165 response to faces generalized completely with respect to the presence or absence of color. The lesions associated with achromatopsia and prosopagnosia have a large overlap and the two syndromes often occur in association (Meadows, 1974b; Zeki, 1991). However, intracranial recordings with strip electrodes (Allison *et al.*, 1994), as well as PET (Ungerleider, 1995) and fMRI (Hadjikhani *et al.*, 1998) studies, have found that face-selective responses are generally more lateral than the color-selective responses. The current study indicates that, despite their anatomical proximity, input from the color area appears to play no role in activating the face area.

The greater OT165 activation to faces presented as digitized photographs, as compared to sketches, corresponds to previous behavioral studies showing superior processing of face-photographs (Davies *et al.*, 1978). Behavioral studies have also found that face-processing is relatively more sensitive to surfaces and gradients, in contrast to object-processing, which is more sensitive to lines and edges (Bruce and Humphreys, 1994). In the current study, meaningless images with color or grayscale gradients activated the OT165 source area more than did meaningless images with black and white lines. Note however, that this difference between graded versus high-contrast control stimuli was much smaller than the difference between faces versus control stimuli. These data suggest that whereas early face-specific processing cannot be secondary to differences in visual processing of edges versus regions, surfaces may play a relatively important role early in the face-encoding process.

Short-latency Occipital Response

In all subjects, the MO-ECD was located at the posterior–inferior occipital midline (in or near the calcarine fissure), suggesting paired generators, symmetrical about the midline. In order to summate, these generators would need to be in horizontally extended cortical surfaces. Maps of human retinotopic cortex suggest ventral V2 and/or VP as the most likely candidates, although a contribution from V1 is also possible (Sereno *et al.*, 1995). The early occipital signals were larger to randomized faces than to the normal faces, and fMRI to the same stimuli as were used in the current study found small decreases in both V1 and V2 to faces as compared with randomized faces (Halgren *et al.*, 1999). This possible V1/V2 generator for the MO-ECD suggests that it may actually result from more contours being present in the randomized than the normal faces, i.e. from inaccurate sensory controls. This hypothesis would also explain why the occipital source is more responsive to the black and white line drawings where the visual information is carried mainly by the outline, as compared with digitized faces, where the information is carried by textural changes. However, the control stimuli appeared to be very well matched for size and contour with the true faces. In order to further explore this problem, the control stimuli were modified to have less contour: the occipital source continued to be present (E. Halgren, T. Raij and R. Hari, unpublished observations). Conversely, the occipital source was not seen when the response to high-contrast swirls was compared with that evoked by the same stimuli after blurring.

If the decreased response to faces is due to the higher-level sensory characteristics that define faces as faces, rather than to a lower-level characteristic such as contour, then the face/nonface distinction must be made very early in visual processing. Even in V1, early experience has strong effects on visual field properties such as ocular dominance and orientation specificity (Hubel and Wiesel, 1970). Faces are important and common visual stimuli from birth, with the behavioral ability to discriminate facial emotions and feature configurations present in human neonates (Meltzoff and Moore, 1977; Field *et al.*, 1982; Flin and Dziurawiec, 1989). Furthermore, especially in unanesthetized animals, long-range visual field interactions on single-cell firing are quite clear, even in V1 (Grinvald *et al.*, 1994; Singer, 1995; Gilbert *et al.*, 1996). It is thus conceivable that the repeated, highly reinforced and prepotent exposure of the developing nervous system to faces results in an altered response profile to the typical arrangement of sensory features that characterize faces.

Surprisingly, the MO-ECD responded significantly differently to emotionally expressive faces, whereas the OT-ECD did not. This differential response occurred very early in MO from 100 to 120 ms post-stimulus onset and then disappeared. A small but systematic difference in sensory characteristics may have been present between faces with neutral versus positive expressions: the teeth are more often exposed in smiling faces. However, no such systematic sensory difference was apparent between the faces with neutral and negative expressions. This apparent capacity to rapidly decode the emotional state of conspecifics could be quite useful for survival in primates. Conceivably, MO110 activity is projected to the amygdaloid formation, which begins to respond to faces at ~120 ms (Halgren *et al.*, 1994a), and could then support the preserved emotional processing of faces sometimes observed in prosopagnosics (Tranel *et al.*, 1988; Bruyer, 1991).

Evidence reviewed above suggests that the MO110 reflects neurons in the V1 and/or V2. Other studies (see below) suggest that the OT165 is generated in the human homologue of TF (Halgren *et al.*, 1999). In monkeys, V2 projects directly to TF, and V1 projects indirectly (via V2 and V4v) to TF (Felleman and VanEssen, 1991). MO activity begins to significantly distinguish between face and nonface stimuli as early as 110 ms post-stimulus onset, and attains maximal amplitude at 127 ms, just before the highly face-specific OT165 response. Compared to the OT165 response, the MO response was more sensitive to the sensory characteristics of the stimuli (i.e. whether they were digitized photographs versus sketches) and generally less sensitive to subtle changes in 'faceness' (e.g. whether facial features were properly arranged). Thus, the probable location, timing and task-correlates of the MO110 suggest that it may perform preliminary processing antecedent to more specific face-encoding during the OT165.

Role of the OT165 within the Face-processing Stream

Using fMRI, the face-selective fusiform area has been shown to be anterior to the retinotopic visual area V4v, and ventromedial to the motion-sensitive areas MT/msTd (Halgren *et al.*, 1999). There is a further retinotopic area encoding both dorsal and ventral visual fields interposed between V4v and the fusiform face area. This topology, as well as this area's cytoarchitectonics and its location relative to gross anatomical landmarks, all imply that it is homologous to area TF (or possibly CITv) of monkeys. These areas receive their main inputs from V4 and PIT, and project heavily to anteromedial temporal areas including entorhinal and perirhinal cortices, which in turn provide the major inputs to the hippocampal formation (Suzuki, 1996; Murray and Bussey, 1999). Together, these later areas constitute the critical anatomical substrate for forming new declarative memories of faces (Corkin, 1984). Through these projections, TF is also a major source of afferents to the amygdala and ventrolateral prefrontal cortex, crucial for the emotional

interpretation of faces (Halgren and Marinkovic, 1995). The anteromedial temporal cortex itself is increasingly implicated in naming familiar faces and recalling information about the person portrayed (Damasio *et al.*, 1996; Eslinger *et al.*, 1996). Direct feedback connections also course from TF to V4v, PITv and even V1, allowing top-down influences on basic perceptual processes (Felleman and VanEssen, 1991; Rockland and Van Hoesen, 1994).

The peak latency of the OT activation at 165 ms places it after the exogenous sensory responses that are generated in early visual cortical regions, and before the cognitive responses modulated by mnestic, emotional and high-level contextual variables. Cognitive modulation of evoked potentials can be seen as early as N220 and N300, but is most prominent during N400 (Halgren, 1990, 1994). These potentials are generated in multiple limbic and association cortical structures, especially the hippocampal, rhinal, inferotemporal and ventrolateral prefrontal cortices (Smith *et al.*, 1986; Halgren *et al.*, 1994a,b; McCarthy *et al.*, 1995; Marinkovic *et al.*, 1999). The cognitive correlates, timing and generators of N400 suggest that it embodies the cognitive integration of the stimulus, relating it to short-term and remote memories, evaluating it for emotional significance, and placing it into the current cognitive context. The N400 is generally evoked in these areas by all potentially semantic stimuli, including words, faces and objects (Halgren *et al.*, 1994a,b) [but exceptions have been noted (McCarthy *et al.*, 1995; Marinkovic *et al.*, 1999)]. Thus, the highly-specific OT165 activation to faces is interpolated between early visual cortical processing and later relatively nonspecific cognitive processing.

Prosopagnosia has been classified as either apperceptive or mnestic (Hecaen, 1981; De Renzi *et al.*, 1991). In apperceptive prosopagnosia, a perceptual deficit is thought to prevent the encoding of the face in a form that is sufficiently precise for activating its relevant memories; in mnestic prosopagnosia, it is hypothesized that access to the face memory trace, or the trace itself, is damaged. The location and timing of the OT165 are consistent with it representing the neural processing stage that is disrupted in apperceptive prosopagnosia. However, the very high face-specificity of the OT165 is not consistent with the lack of specificity that has sometimes been posited for the perceptual deficit in apperceptive prosopagnosia (Young and Bruce, 1991; De Renzi *et al.*, 1991).

A related theoretical approach holds that agnosias arise from *disconnections* between low-level, general-purpose perceptual processors and high-level, general-purpose semantic/verbal response generation mechanisms, i.e. without an intervening stage associated with face perception *per se* (Geschwind, 1965). This theory is clearly inconsistent with the current results demonstrating a face-specific processor that is anatomically and temporally situated between early retinotopic visual cortices and later multimodal cortices that perform cognitive integration.

In conclusion, the current findings seem broadly consistent with the MO127 and OT165 embodying successive stages of a face-encoding process, translating between the sensory code and cognitive processing. This encoding permits the face to be analyzed by other structures such as the inferotemporal cortex (for semantic memory), hippocampal formation (for recent declarative memory), amygdala (for emotional significance) and orbital cortex (for integration with primary memory and psychosocial context). Physiologically, this would correspond to the distinction between the face-selective but memory-insensitive fusiform gyrus activation at 165 ms, followed by the face-insensitive but memory-selective ventral frontotemporal activation with peaks at 460 and 620 ms. The great selectivity of OT165 for human faces as opposed to objects, animal faces or bodies implies that the visual system uses different routes for the analysis of different complex stimuli. In this view, the fusiform gyrus functions as an entry-point to the semantic system for faces, rather than as the semantic system itself. Fusiform lesions would thus prevent both the specific encoding of faces, and the distribution of this information to widespread association and limbic areas where its semantic significance would be probed.

Notes

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