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Time course of superior temporal sulcus activity in response to eye gaze: a combined fMRI and MEG study

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The human superior temporal sulcus (STS) has been suggested to be involved in gaze processing, but temporal data regarding this issue are lacking. We investigated this topic by combining fMRI and MEG in four normal subjects. Photographs of faces with either averted or straight eye gazes were presented and subjects passively viewed the stimuli. First, we analyzed the brain areas involved using fMRI. A group analysis revealed activation of the STS for averted compared to straight gazes, which was confirmed in all subjects. We then measured brain activity using MEG, and conducted a 3D spatial filter analysis. The STS showed higher activity in response to averted versus straight gazes during the 150–200 ms period, peaking at around 170 ms, after stimulus onset. In contrast, the fusiform gyrus, which was detected by the main effect of stimulus presentations in fMRI analysis, exhibited comparable activity across straight and averted gazes at about 170 ms. These results indicate involvement of the human STS in rapid processing of the eye gaze of another individual.

Keywords: functional magnetic resonance imaging (fMRI); fusiform gyrus; gaze; magnetoencephalography (MEG); spatial filter analysis; superior temporal sulcus (STS)

The gaze of another individual can be rapidly processed in the observer's mind. Through evolution, the ability to rapidly process the gaze direction of other individuals would have conferred adaptive value for humans, allowing immediate detection of biologically relevant stimuli in the environment (e.g. predatory animals), and subsequent collective responses to such stimuli. Consistent with this idea, recent experimental studies in psychology have demonstrated that the gaze direction of other individuals is rapidly processed and reflexively triggers an attentional shift (Langton *et al.*, 2000).

Neuroscientific studies in monkeys have explored the neural basis for gaze processing, and have consistently indicated the involvement of the superior temporal sulcus (STS). For example, a single unit recording study in monkeys showed that specific cells in the STS were discharged in response to specific gaze directions (Perrett *et al.*, 1985), and a lesion study in monkeys showed that damage to the STS impaired the discrimination of eye gaze direction (Campbell *et al.*, 1990).

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Also, in humans, several neuroimaging studies using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have described activation of the posterior STS in the processing of eye gaze (Puce *et al.*, 1998; Wicker *et al.*, 1998; Hoffman and Haxby, 2000; Hooker *et al.*, 2003; Pelphrey *et al.*, 2003). For example, an fMRI study showed that averted gazes caused more activation in the posterior STS than did straight gazes (Hoffman and Haxby, 2000). It has been proposed that the posterior STS in humans is homologous to the STS area in monkeys (Allison *et al.*, 2000). Lesion studies in humans have also shown that damage to the temporal cortices, including the posterior STS, impaired the discrimination of gaze direction (Akiyama *et al.*, 2006a) and the attentional shift in response to averted gaze (Akiyama *et al.*, 2006b). These data indicate the involvement of the STS in gaze processing in humans.

However, the time course of STS activity in gaze processing is unknown. Some previous studies (Puce *et al.*, 2000; Watanabe *et al.*, 2002) recorded event-related potentials (ERPs), which characterize neural activity with high temporal resolution, and revealed that the scalp electrodes on the lateral posterior regions showed a peak at about 170 ms in response to gaze aversion, or for averted *vs* straight gazes. These results suggest the involvement of the temporal cortices at around 170 ms in gaze processing. However, as the spatial resolution of ERP is limited (Dale and Sereno, 1993), the exact brain area of this rapid activity remains unclear.

Another study (Watanabe *et al.*, 2001) investigated this issue using magnetoencephalography (MEG), which can provide high temporal resolution with relatively high spatial resolution, compared to ERP (Dale and Sereno, 1993). The study searched for single or double current dipoles, and found activity for gaze aversion at around 170 ms, not in the STS, but in the MT/V5 region. Thus, while some evidence suggests the activity of the human posterior cortices in response to eye gaze at around 170 ms, there is no evidence that the STS is involved in such rapid gaze processing.

Several neuroimaging studies have revealed that within the visual cortices, the lateral posterior fusiform gyrus (FG) is involved in the processing of faces (Puce *et al.*, 1995; Kanwisher *et al.*, 1997). In contrast to STS activity, the studies revealed that the FG is not related to gaze processing (Puce *et al.*, 1998; Hoffman and Haxby, 2000; Hooker *et al.*, 2003). For example, Hoffman and Haxby (2000) reported that a face's gaze direction had no effect on FG activity. Some ERP and MEG studies with dipole fitting reported that in face processing the FG showed a peak at around 170 ms (Halgren *et al.*, 2000; Lewis *et al.*, 2003; Rossion *et al.*, 2003; Deffke *et al.*, 2007). It would therefore be interesting to compare STS and FG activity at around 170 ms during gaze processing.

The purpose of the present study was to investigate the time course of human neural activity in response to averted versus straight gazes combining fMRI and MEG. The combination of hemodynamic and electromagnetic measures of the brain activity complement each other and provide high resolution in both the spatial and temporal domains (Dale and Halgren, 2001; Shibasaki, 2008).

First, to localize the brain regions involved with high spatial resolution, we measured brain activity using fMRI. As in a previous fMRI study (Hoffman and Haxby, 2000), photographs of faces with either averted or straight gazes were presented (Figure 1) and subjects were asked to passively view the stimuli. We identified brain regions that were more active in response to the averted gazes than to straight gazes.

We then measured brain activity while viewing the same stimuli using MEG. To heighten the spatial resolution of the MEG data, we implemented a MEG 3D spatial filter analysis (Toyama *et al.*, 1999). This technique combines the high temporal resolution of MEG with the high spatial resolution achieved by using MRI-constrained spatial filters to measure the direction and intensity of magnetic fields that are generated during brain activity (Toyama *et al.*, 2001). Such analysis using spatial filters has been shown to overcome some problems of traditional MEG analyses with regard to spatial resolution, such as estimating only major current sources contributing to the MEG at particular moments (Dale and Sereno, 1993; Tesche *et al.*, 1995). By applying spatial filter analysis, we analyzed the time course of STS activity, the location of which was identified through fMRI analyses, in response to averted *vs* straight gazes. To compare these conditions, we analyzed FG time courses, which were identified through the main effect of stimulus presentations in fMRI analyses. We predicted that the STS would show greater activity in response to averted *vs* straight gazes at around 170 ms, whereas the FG might not.

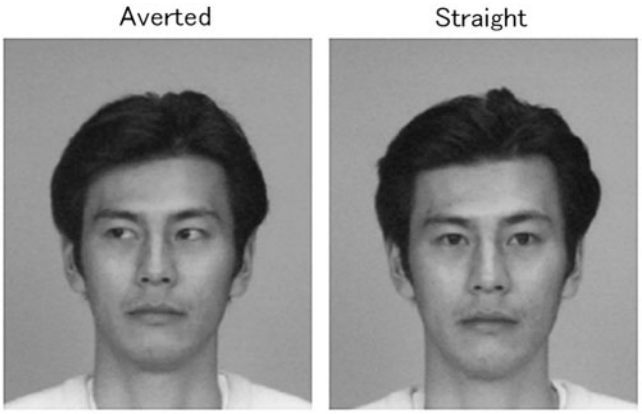

Fig. 1 Illustrations of stimuli.

MATERIALS AND METHODS

Subjects

Four volunteers (two females and two males; mean ± s.d. age 29.0 ± 10.4 years) participated in the study. All subjects were right handed and had normal or corrected-to-normal visual acuity. All subjects gave informed consent to participate in the study, which was conducted in accordance with the institutional ethical provisions and the Declaration of Helsinki.

Experimental design

The experiment involved a within-subject one-factorial design using gaze direction (averted *vs* straight).

Stimuli

The stimuli were chosen from a database set of faces, which contained facial images of changing facial expressions and gaze directions posed by more than 50 Japanese models. Color images of five men and five women with full-face neutral expressions and averted or straight gaze directions were selected (Figure 1). Under the averted gaze condition, the stimulus persons looked ~30° to their right. Mirror images of all the stimuli were also prepared. The stimuli were presented to subtend a visual angle of about 12.0° vertical × 8.0° horizontal.

fMRI presentation apparatus

The events were controlled by SuperLab software (version 2.0; Cedrus, San Pedro, CA, USA). The stimuli were projected from a liquid crystal projector (DLA-G11; Victor Company, Tokyo, Japan) onto a mirror that was positioned in a scanner in front of the subjects.

fMRI procedure

The fMRI experiment utilized a block design as in a previous study (Hoffman and Haxby, 2000). Each subject participated in three experimental sessions. Each session lasted 8 min and consisted of eight 30 s epochs with eight 30 s rest periods interleaved, during which time a fixation point was presented in the center of the screen. In each epoch, the 10 stimuli (each lasting 500 ms) were presented twice. An interstimulus interval of 1000 ms was used to prevent any apparent motion caused by consecutive presentations of stimuli. Each of the two stimulus conditions (averted, straight) was presented in four different epochs within each scan. The order of the stimuli within each epoch was randomized, and the order of epochs within each session was counterbalanced across subjects.

Subjects were instructed to observe the images carefully while fixating on the center of the screen (i.e. where the fixation point was presented during the rest periods). To avoid activations caused by intentional evaluation of stimuli or response selection, subjects were asked to view the stimuli passively, without making any response.

To confirm that brain activation was not explained by eye movement artifacts, we preliminarily tested the subjects while monitoring eye movement in the scanner without image acquisition. The stimuli were presented, and horizontal eye movements were monitored with the MR-Eyetracker (Cambridge Research Systems, Rochester, UK). The number of horizontal eye movements exceeding 5° was very small under all conditions (<0.5 for an epoch), and did not differ significantly across conditions ($P > 0.1$, Friedman's one-way analysis of variance).

fMRI acquisition

Image scanning was performed on a 1.5 T scanning system (MAGNEX ECLIPSE 1.5 T Power Drive 250; Shimadzu Marconi, Kyoto, Japan) using a standard radio-frequency head coil for signal transmission and reception. A forehead pad was used to stabilize the head position. The functional images consisted of 52 consecutive slices parallel to the anteroposterior commissure plane, covering the whole brain. A T2*-weighted gradient echo-planar imaging sequence was used with the following parameters: TR/TE = 6000/60 ms; FA = 90°; matrix size = 64 × 64; voxel size = 3 × 3 × 3 mm^3. Before the acquisition of functional images, a T2-weighted anatomical image was obtained in the same plane as the functional images using a fast spin echo sequence (TR/TE = 9478/80 ms, FA = 90°; matrix size = 256 × 256; voxel size = 0.75 × 0.75 × 3 mm^3; number of echoes = 16). An additional high-resolution T1-weighted anatomical image was also obtained to overlap the MRI and MEG coordinate system, using a 3-D RF-FAST sequence (TR/TE = 12/4.5 ms; FA = 20°; matrix size = 256 × 256; voxel dimension = 1 × 1 × 1 mm^3) after functional image acquisition.

fMRI analysis

Image and statistical analyses were performed using the statistical parametric mapping package SPM99 (http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB6.5 (Mathworks Inc., Sherborn, MA, USA). First, to correct for head movements, functional images of each run were realigned using the first scan as a reference. Data from all subjects showed small motion corrections (<1 mm).

For the group analysis, T2-weighted anatomical images scanned in planes identical to the functional imaging slice were coregistered to the first scan in the functional images. Then, the coregistered T2-weighted anatomical image was normalized to a standard T2 template image, as defined by the Montreal Neurological Institute, involving linear and nonlinear 3D transformations. The parameters from this normalization process were then applied to each of the functional images. These spatially normalized functional images were resampled to a voxel size of 2 × 2 × 2 and smoothed with an isotopic Gaussian kernel (6 mm) to compensate for anatomic variability among subjects. Then activated voxels were searched using the fixed effect model (Friston *et al.*, 1994; Worsley and Friston, 1995). Task-related neural activities under each condition were modeled with a boxcar function, convoluted with a canonical hemodynamic response function. A band-pass filter composed of a discrete cosine-basis function, with a cutoff period of 240 s for the high-pass filter, and a canonical hemodynamic response function for the low-pass filter, was applied. Planned comparisons were first performed to test averted *vs* straight gazes, and then to test the main effect of stimulus presentations. Contrast images were generated for each comparison and then entered into a one-sample *t*-test to create a random effect SPM {*T*}. Voxels were identified as significantly activated with the height threshold of $P < 0.001$ (uncorrected) and the extent threshold corrected for multiple comparisons of the entire brain volume ($P < 0.05$).

For individual analyses, an almost identical procedure was used, with two exceptions. First, both the T1 anatomical images were also coregistered to the functional images. Second, the images were not normalized. For the posterior STS and FG, voxels were identified as significantly activated if they reached the height threshold of $P < 0.001$ (uncorrected). The activation foci were used as the regions of interest (ROIs) in subsequent MEG analyses. When bilateral activation was detected in a single subject, a single hemisphere was selected based on the *T*-value. Note that previous neuroimaging studies reported that individual analyses could show unilateral STS/FG activity in either the left or right hemisphere (Hoffman and Haxby, 2000; Puce *et al.*, 1995). For descriptive purposes, the analyses were also conducted after normalization.

MEG presentation apparatus

The events were controlled by SuperLab software (version 2.0; Cedrus, San Pedro, CA, USA). The stimuli were

presented by a projector (LP-9200; Sanyo, Tokyo, Japan) onto the back of a transparent screen.

MEG acquisition

The experiment was conducted in an electromagnetically shielded room. Four calibration coils (NiCl) were mounted bilaterally on the temporal skin (two each for superior superciliary and anterior subauricular regions) of the subjects. Optical calibration using a 3D digital camera (VIVID700; Minolta, Tokyo, Japan) and electromagnetic calibration, passing currents (19–263 μA, 10 Hz) through the coils, were conducted at the beginning of the recording session (cf. Kajihara *et al.*, 2004). The coordinates for MEG and the T1-weighted anatomical MRI were superimposed using the information on cranium contours and coil positions.

MEG acquisition was performed using a 201-channel, whole-head biomagnetic imaging system (SBI-200; Shimadzu, Kyoto, Japan). A chin pad was used to stabilize head position. Data were sampled by an amplifier for 1000 ms at 1000 Hz (100 samples for the prestimulus baseline), through a band-pass of 0.01–100 Hz, and averaged for each type of condition. A notch filter was used to remove 60 Hz interference. The signal was further filtered offline through a 30 Hz low-pass filter.

MEG procedure

Each subject participated in two experimental sessions, with a long break between the two sessions. Each session contained 280 presentations of averted and straight gaze conditions, for a total of 560 images per subject. The stimuli were presented in random order.

In each trial, the stimulus was presented for 500 ms in central vision. A small cross as a warning signal preceded the stimulus presentation for 1000 ms. The subjects were instructed to passively view the stimuli and also not to blink until the stimuli had disappeared. Intertrial intervals were randomly changed from 500 to 1000 ms. Subjects had a short rest when 80 trials were finished. Before data collection, subjects were familiarized with the procedure through a block of more than 200 training trials.

MEG analysis

The analyses were conducted using software created by Shimadzu (Kyoto, Japan) implemented on an Unix computer. Spatial filter analyses using spherical lead field models with regularly spaced 21×21 current dipoles on a hemisphere were conducted. In the model, dipoles were spaced 9° apart. Spatial filters focusing on the ROIs were analyzed. The ROIs in each subject were specified by the coordinates of the STS and FG, which were identified through fMRI individual analyses using the contrast between averted *vs* straight gaze and the main effect, respectively. To assess STS and FG signals, we first examined the mean intensity of the region in each 50 ms time window from 0 to 300 ms (0–50, 50–100, 100–150, 150–200, 200–250, 250–300 ms). These time regions were analyzed based on previous behavioral data indicating that the effect of gaze can be apparent in behavior earlier than 400 ms after stimulus presentation (Okada *et al.*, 2003). Then, for time windows that differed significantly between gaze conditions, we identified the peaks and analyzed their amplitudes and latencies. For these analyses, we conducted Wilcoxon's signed-ranks test (nonparametric analysis corresponding to parametric paired *t*-tests) for averted versus straight gaze, as the distribution of the intensities did not show normality. Values were deemed statistically significant when $P < 0.05$.

Table 1 Brain regions showing significant activation in response to averted *vs* straight gaze

Brain region	BA	Coordinates			*T*-value
		x	*y*	*z*	
R. Superior temporal sulcus	39	54	−66	16	5.23
R. Parahippocampal gyrus	19	30	−52	−10	5.27
L. Angular gyrus	39	−30	−58	34	5.33
L. Superior temporal sulcus	37	−44	−62	18	5.80
L. Superior frontal gyrus	10	−4	60	−4	5.13
L. Cerebellum	–	0	−62	−22	5.11

The coordinates of activation foci in the MNI system and their *T*-values are shown.

RESULTS

fMRI

The group analysis revealed significant bilateral activation of the STS in response to averted *vs* straight gaze (Table 1; Figure 2A). Other significant areas of activation included the parahippocampal gyrus in the right hemisphere and the angular gyrus, medial frontal gyrus and cerebellum in the left hemisphere (Table 1). No other significant areas of activation were detected. Specifically, area MT/V5, which is located in the ascending limb of the inferior temporal sulcus (Tootell *et al.*, 1997; Watson *et al.*, 1993), did not show significant activity. No significant activation was observed when we compared straight *vs* averted gaze. Stimulus presentation had a main effect of significant activation among broad ranges of bilateral posterior regions, including the FG activation foci (Figure 3A).

The individual analyses revealed significant activation of the corresponding STS area in either the left or right hemisphere of all subjects when we compared averted *vs* straight gaze (Table 2; Figure 4A). This was also the case for the main effect of stimulus presentations in the FG (Table 2; Figure 4A).

MEG

Figure 2B shows the grand average waves for the intensity of the STS activity in response to averted and straight gazes. Prominent peaks occurred at about 170 ms, and were

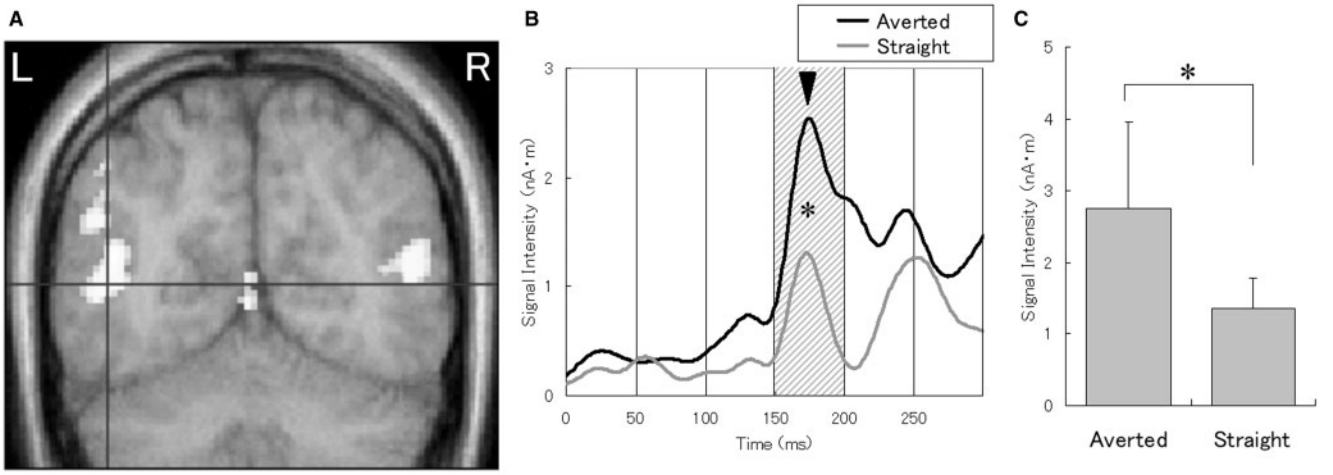

Fig. 2 (**A**) Statistical parametric map showing STS activity for averted *vs* straight gazes identified in a group analysis. The activation is overlaid on the spatially normalized anatomical MRI of the mean brain of the subjects. (**B**) The grand average current intensity of STS activity. The arrowhead indicates the peak of interest at about 170 ms. A shaded time zone with an asterisk indicates a significant difference in the mean intensity between averted and straight gazes ($P < 0.05$). (**C**) Mean (with SEM) peak amplitudes of STS at about 170 ms from stimulus onset.

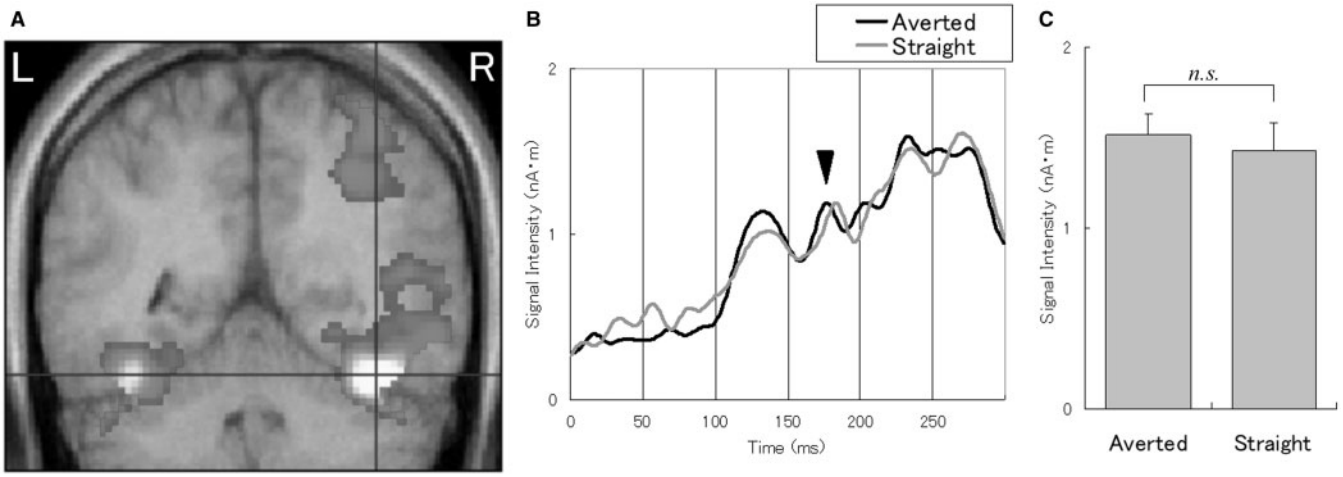

Fig. 3 (**A**) Statistical parametric map showing FG activity for the main effect of stimulus presentations identified in a group analysis. The activation is overlaid on the spatially normalized anatomical MRI of the mean brain of the subjects. (**B**) The grand average current intensity of FG activity. The arrowhead indicates the peak of interest at about 170 ms. (**C**) Mean (with SEM) peak amplitudes of FG at about 170 ms from stimulus onset.

Table 2 Activation foci of STS (averted *vs* straight) and FG (main effect) in each subject

Subject no.	STS				FG			
	Coordinates			*T*-value	Coordinates			*T*-value
	x	*y*	*z*		*x*	*y*	*z*	
1	54	−66	18	5.88	32	−58	−16	31.91
2	−44	−60	16	4.16	36	−70	−20	34.85
	44	−58	10	4.05	−36	−70	−18	12.24
3	−52	−52	14	5.33	34	−58	−18	21.63
					−30	−72	−22	8.84
4	44	−62	16	4.55	26	−74	−16	20.35
	−44	−66	14	3.76				

The normalized coordinates in the MNI system and *T*-values are shown.

observed in all subjects under all conditions. Peaks also appeared at around 250 ms in grand average waves, but these peaks were not consistent across subjects. Differences in peak amplitudes between averted and straight gazes were found at the peak around 170 ms. Wilcoxon's signed-ranks test for the mean intensity of the STS activity revealed a significant difference for averted *vs* straight gazes only at 150–200 ms ($z = 1.85$, $P < 0.05$). Other time windows did not reveal significant differences ($P > 0.1$). Peak analyses of amplitudes during 150–200 ms revealed significantly greater activity in response to averted gazes than to straight gazes (Figure 2C). Peak analyses of latency did not reveal significant differences between averted and straight gazes ($M \pm s.d. = 174.3 \pm 12.3$ and 171.9 ± 4.2 ms for averted and straight gazes, respectively; $P > 0.1$).

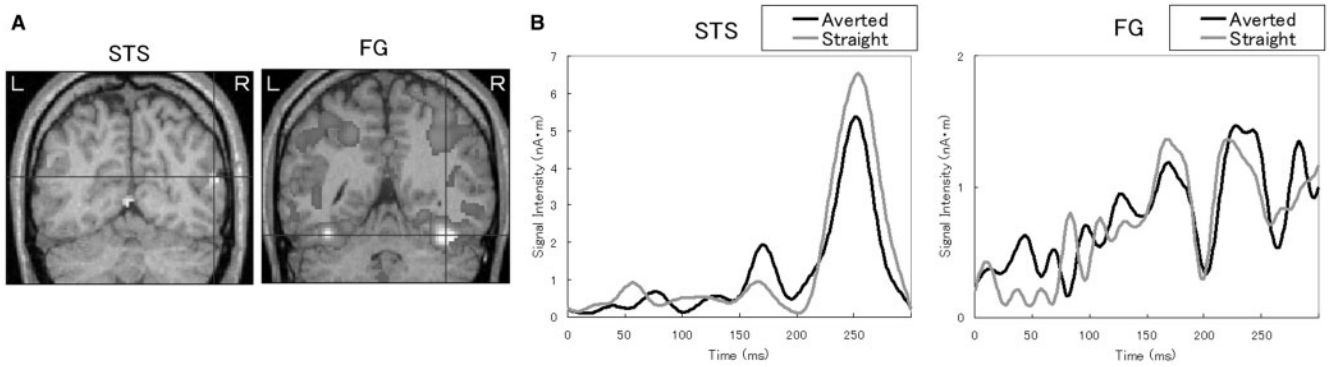

Fig. 4 (**A**) Statistical parametric map of a representative single subject showing STS and FG activity for averted *vs* straight gazes and main effect of stimulus presentations, respectively. The activation is overlaid on a corresponding spatially normalized anatomical MRI. (**B**) Representative current intensity of STS and FG activity in a single subject.

Figure 3B presents the grand average waves for FG activity intensity in response to averted and straight gazes. As with STS activity, prominent peaks appeared at about 170–180 ms, but we observed no differences between gaze conditions. Wilcoxon's signed-ranks test for mean FG activity intensity in time windows revealed no significant differences between averted and straight gazes ($P > 0.1$). We confirmed this result by conducting peak analyses for amplitudes during 150–200 ms; we found no significant differences between averted and straight gazes ($P > 0.1$; Figure 3C). Peak analyses of latency also revealed no significant differences between averted and straight gazes ($M \pm s.d. = 183.5 \pm 16.4$ and 185.3 ± 15.0 ms for averted and straight gazes, respectively; $P > 0.1$).

Figure 4B shows representative examples of the intensity of the STS and FG activity. As some subjects showed bilateral activity in the STS or FG in fMRI individual analyses, we preliminarily compared the MEG activity of these regions across hemispheres using visual inspection and peak analyses. The results showed comparable peak activity at about 170 ms across hemispheres. Given our small sample size, the hemispheric differences are not discussed further.

DISCUSSION

By combining fMRI and MEG studies, we sought to depict the time course of the activity of the STS compared with that of the FG in response to averted *vs* straight gazes. The fMRI study revealed that the posterior STS was more active in response to averted gazes than to straight gazes, consistent with previous neuroimaging studies (Puce *et al.*, 1998; Hoffman and Haxby, 2000; Hooker *et al.*, 2003; Pelphrey *et al.*, 2003). More importantly, the results of the MEG 3D spatial filter analysis revealed that the higher activity in the STS for averted than straight gazes occurred during the 150–200 ms after stimulus onset. Activity in this time window is consistent with previous ERP studies (Puce *et al.*, 2000; Watanabe *et al.*, 2002), which reported that activity for gaze aversion or averted *vs* straight gazes occurred in the posterotemporal cortices at around 170 ms. Since fMRI/PET studies alone lack temporal resolution and ERP studies alone lack spatial resolution (Dale and Halgren, 2001; Shibasaki, 2008), there has been only speculation about the time course of the STS activity that differentiates averted and straight gazes. To the best of our knowledge, this study is the first to show that the human STS become active at around 170 ms in the processing of eye gaze.

Inconsistencies between our results and a previous MEG study (Watanabe *et al.*, 2001), which reported activity in the MT/V5 area for gaze aversion at around 170 ms, may be attributable to methodological differences. First, whereas our study used static gaze stimuli, Watanabe *et al.* (2001) examined dynamic gaze stimuli. The MT/V5 area is known to be involved in visual motion processing (Zeki, 1993). A previous combined fMRI and MEG study reported that the human MT/V5 area showed activity peaking at around 150–180 ms for visual motion changes (Ahlfors *et al.*, 1999). The MT/V5 activity related to gaze aversion observed by Watanabe *et al.* (2001) might have been caused by visual motion during gaze shifting. Second, Watanabe *et al.* (2001) recorded the MEG and searched for single or double current dipoles. In contrast, our study had methodological advantages to heighten the spatial resolution. We measured fMRI to identify the coordinates of the STS activation in response to averted *vs* straight gazes. The spatial resolution of fMRI is superior to that of MEG dipole analyses. Furthermore, we analyzed the MEG data using a 3D spatial filter analysis, which yields higher spatial resolution than traditional MEG analyses (Toyama *et al.*, 1999). It has been proposed that a combination of different brain recording techniques can allow one to overcome the temporal and spatial resolution limitations of each of the imaging techniques (Dale and Sereno, 1993). We believe that the present combination of fMRI and MEG allowed us to heighten both the spatial and temporal resolution of STS activity in response to averted *vs* straight gazes.

The rapid activation of the STS that we found is in line with published psychological data. Experimental psychological studies have demonstrated that another individual's

gaze direction automatically triggers an attentional shift (Langton *et al.*, 2000). Studies have shown that the effect of gaze direction rapidly influences target detection behaviors, which occur at around a few hundred milliseconds from stimulus onset (Langton *et al.*, 2000). In another line of research, a lesion study described the involvement of the STS in gaze-triggered attentional shift (Akiyama *et al.*, 2006b). These data, together with the present finding, suggest that when we observe the gaze of another individual, the neural mechanism involving the STS analyzes the gaze direction rapidly; this occurs specifically at around 150–200 ms, and the data are immediately transmitted into the neural network related to visuospatial attention and can thus influence behavior.

Our analysis did not reveal differences in other time ranges within the STS region. These null findings are consistent with previous scalp ERP recording studies, which did not report significant differences between gaze direction condition at early stages (about 100 ms) or late stages (about 250 ms; Puce *et al.*, 2000). A previous scalp ERP study (Schweinberger *et al.*, 2004) indicated that components at about 250 ms were related to the individual recognition of faces, which supports the finding that STS activity did not change at this time range.

Regarding the STS activation, the implied motion concept provides an alternative interpretation (c.f. Freyd, 1987). Previous fMRI studies revealed that static body images implying motion, such as throwing a discus or jumping, activated the posterior STS (Kourtzi and Kanwisher, 2000; Senior *et al.*, 2000). As the averted, not straight, gaze can imply motion, one might suspect that the higher activation in the STS for averted *vs* straight gazes could be attributed to the processing of implied motion, not to the processing of gaze *per se*. However, the previous studies (Kourtzi and Kanwisher, 2000; Senior *et al.*, 2000) reported that the images with implied motion activated not only the STS, but also the MT/V5 area, for which our fMRI analysis did not reveal significant activation. Furthermore, a previous fMRI study reported that while viewing faces with averted and straight gazes, paying attention to gaze activated the STS more than paying attention to identity did (Hoffman and Haxby, 2000). These data support our interpretation that the STS is related to gaze processing.

Our fMRI and MEG analyses indicated that FG activation did not distinguish gaze direction. This is in line with the results of previous neuroimaging studies, which indicated that gaze direction had no effect on FG activity (e.g. Hoffman and Haxby, 2000). Recent fMRI studies have shown that the FG is involved in facial identity processing (Andrews and Ewbank, 2004; Rotshtein *et al.*, 2005).

Our finding of the different activity patterns between the STS and FG at 150–200 ms has implications for the interpretation of scalp-recorded electromagnetic components for face processing. Several studies have reported that the observation of faces elicits electric/magnetic activity at the temporal sites at around 170 ms (e.g. Bentin *et al.*, 1996), but its cognitive function and neural source are controversial. Some studies have suggested that this face-related component reflects face detection or identification (Xu *et al.*, 2005; Jacques and Rossion, 2006; Harris and Nakayama, 2007), whereas other studies have reported that this component is affected by the gaze direction (Puce *et al.*, 2000; Watanabe *et al.*, 2002). Some studies have estimated the dipole in the FG (Halgren *et al.*, 2000; Lewis *et al.*, 2003; Rossion *et al.*, 2003; Deffke *et al.*, 2007), whereas others have identified the dipoles around the STS (Bentin *et al.*, 1996; Itier and Taylor, 2004). Our data suggest that this posterior scalp electromagnetic activity around 170 ms could reflect the activity of both the STS and FG, which are related to different cognitive processes for faces. A previous combined fMRI and ERP study consistently reported that the amplitude of this face-related ERP component correlated with BOLD signals in both the FG and STS (Horovitz *et al.*, 2004). To clarify the cognitive functions of the scalp-recorded face-related components to faces, one may need to dissociate the signals from multiple neural sources using statistical procedures (e.g. independent component analysis; Makeig *et al.*, 2004).

Our results for the gaze processing may be interpretable in a more generalized framework of face processing. Some theories of the neurocognitive mechanisms for face processing have suggested that the STS and FG are involved in processing of different aspects of faces, specifically changeable and invariant aspects of face, respectively (Haxby *et al.*, 2000; Palermo and Rhodes, 2007). Our findings are consistent with these theories and specify that the different processes could be implemented as early as about 170 ms poststimulus onset. It is interesting that the theories also posited that the STS is involved in processing of the changeable aspects of faces other than gaze direction, such as facial expressions and lipspeech. Consistent with this prediction, a recent fMRI study reported that the processing of facial expressions and gaze direction induced overlapping activation in the STS (Engell and Haxby, 2007). We speculate that the observation of other changeable aspects of faces may activate the STS region at a similar time range as gaze direction does, which could be an interesting issue for future research using our methodology.

We believe that our MEG analysis utilizing the spatial filter dissociated STS activity from that of other brain areas in the visual cortices. A previous study (Toyama *et al.*, 1999) conducted a series of simulation studies to test the spatial resolution of MEG spatial filter analysis. In one experiment, they placed two source dipoles at various distances, and found that spatial filter analysis was generally capable of correctly resolving multiple source dipoles if they were separated by >17 mm; this degree of spatial resolution is almost comparable to that of neuroimaging techniques. Hoffman and Haxby (2000; Experiment 1) examined relationships between the STS and FG, and provided information about

the distance between them. Their results indicated that the distance between the STS and FG was about 29–34 mm. Puce *et al.* (1998) examined relationships between the STS and MT/V5, and provided information about the distance between them. They found the distance between the STS and MT/V5 was about 19–25 mm. These data suggest that activity in the STS and FG or MT/V5 was dissociated in the MEG spatial filter analyses. Our data support this idea, revealing that STS activity increased in response to averted *vs* straight gazes, whereas FG activity did not.

We used a methodology that combined hemodynamic and electromagnetic measures. This approach can heighten both the spatial and temporal resolution of brain activity compared to the use of a single modality (Dale and Halgren, 2001; Shibasaki, 2008). Several previous studies have demonstrated the effectiveness of this integrated strategy for visual processing (e.g. Ahlfors *et al.*, 1999) and more specifically for visual face processing (e.g. Horovitz *et al.*, 2004). Our results extend the notion for gaze processing.

There are some alternative methods that combine different modalities, which have characteristic advantages and disadvantages (Shibasaki, 2008). For example, whereas we first analyzed the fMRI and then used the ROI information for the MEG analyses, there are some proposals regarding a generalized framework for the analyses using both modalities. For example, Sato *et al.* (2004a) proposed a hierarchical Bayesian analysis that uses the covariance matrix of fMRI activation as a prior to estimate the spatial filters of the MEG. However, these integrated analysis methods are very novel and still need to be validated. Therefore, we coupled conventional and validated analyses for each modality, as in some previous studies (Brunetti *et al.*, 2008). Since the strategy of combining different neuroimaging modalities is evolving rapidly, future methodological modifications may provide more valuable findings.

An important assumption when combining fMRI and MEG should be mentioned. This strategy is based on the assumption that the neural networks involved in inducing a measured signal are identical. This assumption is in line with data for monkeys (Logothetis *et al.*, 2001) and humans (Arthurs and Boniface, 2003), indicating that hemodynamic responses correlate positively with field potentials. However, these signal-generating mechanisms could differ. For example, Mathiak and Fallgatter (2005) pointed out that, whereas an fMRI signal might reflect inhibitory postsynaptic activity, an MEG signal might not. Future methodological research is required to confirm the validity of the assumptions on which the combined MEG and fMRI technique is based.

Some limitations of the present study must be acknowledged. First, we analyzed only STS and FG with our specific hypotheses. We adopted this ROI approach because MEG has the disadvantage of being insensitive to deep or radially oriented sources (Dale and Sereno, 1993), which restricts depiction of brain activity. Our preliminary analysis of the activity in some brain regions (e.g. the angular gurus) did not reveal evident peaks. Furthermore, MEG spatial filter analysis lacks a means to normalize entire brain activity among subjects. It is possible that by using MEG we overlooked important differences in brain activity. Previous neuroimaging studies have shown the involvement of some other brain regions in gaze processing. For example, studies have reported activity in the intraparietal sulcus (Hoffman and Haxby, 2000) and medial frontal gyrus (Calder *et al.*, 2002) while subjects viewed averted gazes. Other studies have demonstrated that the amygdala is involved in gaze processing (Kawashima *et al.*, 1999; Sato *et al.*, 2004b). Although activity in these brain regions appears inconsistent across studies relative to that in the STS, analysis of temporal data from these regions will be required in future studies. Second, although we obtained reliable findings using four participants, the small-sample approach lacks statistical power. It would be desirable to confirm that some nonsignificant differences in our MEG analyses (e.g. activity at early stages) could be replicated with more participants.

In summary, we obtained fMRI and MEG images while subjects viewed images of faces with averted and straight gazes. The results of fMRI revealed higher activity in the posterior STS in response to averted versus straight gazes. The results of the MEG 3D spatial filter analysis revealed that the STS showed higher activity in response to averted *vs* straight gazes during the 150–200 ms after stimulus onset, peaking at around 170 ms. These results indicate that the human STS is involved in rapid processing of the eye gaze of another individual.

REFERENCES

Ahlfors, S.P., Simpson, G.V., Dale, A.M., et al. (1999). Spatiotemporal activity of a cortical network for processing visual motion revealed by MEG and fMRI. *Journal of Neurophysiology*, *82*, 2545–2555.

Akiyama, T., Kato, M., Muramatsu, T., Saito, F., Nakachi, R., Kashima, H. (2006a). A deficit in discriminating gaze direction in a case with right superior temporal gyrus lesion. *Neuropsychologia*, *44*, 161–170.

Akiyama, T., Kato, M., Muramatsu, T., Saito, F., Umeda, S., Kashima, H. (2006b). Gaze but not arrows: a dissociative impairment after right superior temporal gyrus damage. *Neuropsychologia*, *44*, 1804–1810.

Allison, T., Puce, A., McCarthy, G. (2000). Social perception from visual cues: role of the STS region. *Trends in Cognitive Science*, *4*, 267–278.

Andrews, T.J., Ewbank, M.P. (2004). Distinct representations for facial identity and changeable aspects of faces in the human temporal lobe. *NeuroImage*, *23*, 905–913.

Arthurs, O.J., Boniface, S.J. (2003). What aspect of the fMRI BOLD signal best reflects the underlying electrophysiology in human somatosensory cortex? *Clinical Neurophysiology*, *114*, 1203–1209.

Bentin, S., Allison, T., Puce, A., Perez, E., McCarthy, G. (1996). Electrophysiological studies of face perception in humans. *Journal of Cognitive Neuroscience*, *8*, 551–565.

Brunetti, M., Della Penna, S., Ferretti, A., et al. (2008). A frontoparietal network for spatial attention reorienting in the auditory domain: a human fMRI/MEG study of functional and temporal dynamics. *Cerebral Cortex*, *18*, 1139–47.

Calder, A.J., Lawrence, A.D., Keane, et al. (2002). Reading the mind from eye gaze. *Neuropsychologia*, *40*, 1129–1138.

Campbell, R., Heywood, C.A., Cowey, A., Regard, M., Landis, T. (1990). Sensitivity to eye gaze in prosopagnosic patients and monkeys with superior temporal sulcus ablation. *Neuropsychologia*, *28*, 1123–1142.

Dale, A.M., Halgren, E. (2001). Spatiotemporal mapping of brain activity by integration of multiple imaging modalities. *Current Opinion in Neurobiology*, *11*, 202–208.

Dale, A.M., Sereno, M. (1993). Improved localization of cortical activity by combining EEG and MEG with MRI cortical surface reconstruction. *Journal of Cognitive Neuroscience*, *5*, 162–176.

Deffke, I., Sander, T., Heidenreich, J., et al. (2007). MEG/EEG sources of the 170-ms response to faces are co-localized in the fusiform gyrus. *NeuroImage*, *35*, 1495–1501.

Engell, A.D., Haxby, J.V. (2007). Facial expression and gaze-direction in human superior temporal sulcus. *Neuropsychologia*, *45*, 3234–3241.

Freyd, J.J. (1987). Dynamic mental representations. *Psychological Review*, *94*, 427–438.

Friston, K.J., Jezzard, P., Turner, R. (1994). Analysis of functional MRI time-series. *Human Brain Mapping*, *1*, 153–171.

Halgren, E., Raij, T., Marinkovic, K., Jousmaeki, V., Hari, R. (2000). Cognitive response profile of the human fusiform face area as determined by MEG. *Cerebral Cortex*, *10*, 69–81.

Harris, A., Nakayama, K. (2007). Rapid face-selective adaptation of an early extrastriate component in MEG. *Cerebral Cortex*, *17*, 63–70.

Haxby, J.V., Hoffman, E.A., Gobbini, M.I. (2000). The distributed human neural system for face perception. *Trends in Cognitive Sciences*, *4*, 223–233.

Hoffman, E.A., Haxby, J.V. (2000). Distinct representations of eye gaze and identity in the distributed human neural system for face perception. *Nature Neuroscience*, *3*, 80–84.

Hooker, C.I., Paller, K.A., Gitelman, D.R., Parrish, T. B., Mesulam, M.M., Reber, P.J. (2003). Brain networks for analyzing eye gaze. *Brain Research Cognitive Brain Research*, *17*, 406–418.

Horovitz, S.G., Rossion, B., Skudlarski, P., Gore, J.C. (2004). Parametric design and correlational analyses help integrating fMRI and electrophysiological data during face processing. *Neuroimage*, *22*, 1587–1595.

Itier, R.J., Taylor, M.J. (2004). Source analysis of the N170 to faces and objects. *Neuroreport*, *15*, 1261–1265.

Jacques, C., Rossion, B. (2006). The speed of individual face categorization. *Psychological Science*, *17*, 485–492.

Kajihara, S., Ohtani, Y., Goda, N., Tanigawa, M., Ejima, Y., Toyama, K. (2004). Wiener filter-magnetoencephalography of visual cortical activity. *Brain Topography*, *17*, 13–25.

Kanwisher, N., McDermott, J., Chun, M.M. (1997). The fusiform face area: a module in human extrastriate cortex specialized for face perception. *Journal of Neuroscience*, *17*, 4302–4311.

Kawashima, R., Sugiura, M., Kato, T., et al. (1999). The human amygdala plays an important role in gaze monitoring. A PET study. *Brain*, *122*, 779–783.

Kourtzi, Z., Kanwisher, N. (2000). Activation in human MT/MST by static images with implied motion. *Journal of Cognitive Neuroscience*, *12*, 48–55.

Langton, S.R.H., Watt, R.J., Bruce, V. (2000). Do the eyes have it? Cues to the direction of social attention. *Trends in Cognitive Sciences*, *4*, 50–59.

Lewis, S., Thoma, R.J., Lanoue, M.D., et al. (2003). Visual processing of facial affect. *NeuroReport*, *14*, 1841–1845.

Logothetis, N.K., Pauls, J., Augath, M., Trinath, T., Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature*, *412*, 150–157.

Makeig, S., Debener, S., Onton, J., Delorme, A. (2004). Mining event-related brain dynamics. *Trends in Cognitive Sciences*, *8*, 204–210.

Mathiak, K., Fallgatter, A.J. (2005). Combining magnetoencephalography and functional magnetic resonance imaging. *International Review of Neurobiology*, *68*, 121–148.

Okada, T., Sato, W., Murai, T., Kubota, Y., Toichi, M. (2003). Eye gaze triggers visuospatial attentional shift in individuals with autism. *Psychologia*, *46*, 246–254.

Palermo, R., Rhodes, G. (2007). Are you always on my mind? A review of how face perception and attention interact. *Neuropsychologia*, *45*, 75–92.

Pelphrey, K.A., Morris, J.P., McCarthy, G. (2005). Neural basis of eye gaze processing deficits in autism. *Brain*, *128*, 1038–1048.

Pelphrey, K.A., Singerman, J.D., Allison, T., McCarthy, G. (2003). Brain activation evoked by perception of gaze shifts: the influence of context. *Neuropsychologia*, *41*, 156–170.

Perrett, D.I., Smith, P.A., Potter, D.D., et al. (1985). Visual cells in the temporal cortex sensitive to face view and gaze direction. *Proceedings of the Royal Society of London Series B*, *223*, 293–317.

Puce, A., Allison, T., Gore, J.C., McCarthy, G. (1995). Face-sensitive regions in human extrastriate cortex studied by functional MRI. *Journal of Neurophysiology*, *74*, 1192–1199.

Puce, A., Allison, T., Bentin, S., Gore, J.C., McCarthy, G. (1998). Temporal cortex activation in humans viewing eye and mouth movements. *Journal of Neuroscience.*, *18*, 2188–2199.

Puce, A., Smith, A., Allison, T. (2000). ERPs evoked by viewing facial movements. *Cognitive Neuropsychology*, *17*, 221–239.

Rossion, B., Joyce, C.A., Cottrell, G.W., Tarr, M.J. (2003). Early lateralization and orientation tuning for face, word, and object processing in the visual cortex. *NeuroImage*, *20*, 1609–1624.

Rotshtein, P., Henson, R.N., Treves, A., Driver, J., Dolan, R.J. (2005). Morphing Marilyn into Maggie dissociates physical and identity face representations in the brain. *Nature Neuroscience*, *8*, 107–113.

Sato, M., Yoshioka, T., Kajihara, S., et al. (2004a). Hierarchical Bayesian estimation for MEG inverse problem. *Neuroimage*, *23*, 806–826.

Sato, W., Yoshikawa, S., Kochiyama, T., Matsumura, M. (2004b). The amygdala processes the emotional significance of facial expressions: an fMRI investigation using the interaction between expression and face direction. *NeuroImage*, *22*, 1006–1013.

Schweinberger, S.R., Huddy, V., Burton, A.M. (2004). N250r: a face-selective brain response to stimulus repetitions. *NeuroReport*, *15*, 1501–1505.

Senior, C., Barnes, J., Giampietro, V., et al. (2000). The functional neuroanatomy of implicit-motion perception or representational momentum. *Current Biology*, *10*, 16–22.

Shibasaki, H. (2008). Human brain mapping: hemodynamic response and electrophysiology. *Clinical Neurophysiology*, *119*, 731–43.

Tesche, C.D., Uusitalo, M.A., Ilmoniemi, R.H., Huotilainen, M., Kajola, M., Salonen, O. (1995). Single-space projection of MEG data characterize both distributed and well-localized neuronal sources. Electroencephalogr. *Clinical Neurophysiology*, *95*, 189–200.

Tootell, R.B., Mendola, J.D., Hadjikhani, N.K., et al. (1997). Functional analysis of V3A and related areas in human visual cortex. *Journal of Neuroscience*, *17*, 7060–7078.

Toyama, K., Yoshikawa, K., Yoshida, Y., et al. (1999). A new method for magnetoencephalography: a three-dimensional magnetometer-spatial filter system. *Neuroscience*, *91*, 405–415.

Toyama, K., Yoshikawa, K., Tomita, S., Kajiwara, S. (2001). A new technique in magnetoencephalography and its application to visual neuroscience. In: Nakada, T., editor. *Human Higher Function, I. New Methodologies*. London: Smith-Gordon Publisher, pp. 201–218.

Watanabe, S., Kakigi, R., Puce, A. (2001). Occipitotemporal activity elicited by viewing eye movements: a magnetoencephalographic study. *NeuroImage*, *13*, 351–363.

Watanabe, S., Miki, K., Kakigi, R. (2002). Gaze direction affects face perception in humans. *Neuroscience Letters*, *325*, 163–166.

Watson, J.D., Myers, R., Frackowiak, R.S., et al. (1993). Area V5 of the human brain: evidence from a combined study using positron emission tomography and magnetic resonance imaging. *Cerebral Cortex*, *3*, 79–94.

Wicker, B., Michel, F., Henaff, M.A., Decety, J. (1998). Brain regions involved in the perception of gaze: a PET study. *NeuroImage*, *8*, 221–227.

Worsley, K.J., Friston, K.J. (1995). Analysis of fMRI time-series revisited—again. *NeuroImage*, *2*, 173–181.

Xu, Y., Liu, J., Kanwisher, N. (2005). The M170 is selective for faces, not for expertise. *Neuropsychologia*, *43*, 588–597.

Zeki, S. (1993). *A Vision of the Brain*. Oxford: Blackwell.