Dissociable Roles of the Superior Temporal Sulcus and the Intraparietal Sulcus in Joint Attention: A Functional Magnetic Resonance Imaging Study

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Abstract

■ Previous imaging work has shown that the superior temporal sulcus (STS) region and the intraparietal sulcus (IPS) are specifically activated during the passive observation of shifts in eye gaze [Pelphrey, K. A., Singerman, J. D., Allison, T., & McCarthy, G. Brain activation evoked by perception of gaze shifts: The influence of context. *Neuropsychologia, 41,* 156–170, 2003; Hoffman, E. A., & Haxby, J. V. Distinct representations of eye gaze and identity in the distributed human neural system for face perception. *Nature Neuroscience, 3,* 80–84, 2000; Puce, A., Allison, T., Bentin, S., Gore, J. C., & McCarthy, G. Temporal cortex activation in humans viewing eye and mouth movements. *Journal of Neuroscience, 18,* 2188–2199, 1998; Wicker, B., Michel, F., Henaff, M. A., & Decety, J. Brain regions involved in the perception of gaze: A PET study. *Neuroimage, 8,* 221–227, 1998]. Are the same brain regions also involved in extracting gaze direction in order to establish joint attention? In an event-related functional magnetic resonance imaging experiment, healthy human subjects actively followed the directional cue provided by the eyes of another person toward an object in space or, in the control condition, used a nondirectional symbolic cue to make an eye movement toward an object in space. Our results show that the posterior part of the STS region and the cuneus are specifically involved in extracting and using detailed directional information from the eyes of another person to redirect one's own gaze and establish joint attention. The IPS, on the other hand, seems to be involved in encoding spatial direction and mediating shifts of spatial attention independent of the type of cue that triggers this process. ■

INTRODUCTION

Nonverbal signals play an important role in social interactions. Among the different sources of nonverbal information, the eyes seem to provide most information and draw most attention (Emery, 2000). The ability to extract information from the eyes is crucial for normal social communication. Of particular importance is the ability to determine the precise direction of another person's gaze. It not only provides us salient information about the focus of attention of that person but it also plays a role in more complex forms of social cognition, such as visual perspective-taking, deception, empathy, and "theory of mind" (Emery, 2000). When someone follows the direction of another person's gaze toward an object in space, two persons are attending to the same object and this is termed "joint attention."

In normally developing children, joint attention emerges during the second half of the first year (Bakeman & Adamson, 1984) and is reliably established by 10 to 12 months of age (Corkum & Moore, 1998; Scaife & Bruner, 1975). Gaze processing is disturbed in disorders that effect social cognition like autism. This deficit is not necessarily based on eye-gaze discrimination because children with autism can distinguish between a person looking at them (direct gaze) and a person looking somewhere else (averted gaze) (Baron-Cohen, Campbell, Karmiloff-Smith, Grant, & Walker, 1995). However, they lack or have a severely delayed development of joint attention (Leekam, Lopez, & Moore, 2000; Leekam, Hunnisett, & Moore, 1998). From the different disturbances in gaze processing, joint attention is of particular interest because it is one of the most reliably identified early abnormalities in children with autism (Charman, 2003; Baron-Cohen et al., 1996).

Several sources of evidence, including single-cell recordings, a lesion study in monkeys, and neuroimaging studies in humans, have revealed a cortical region in and near the superior temporal sulcus (STS) being involved in the perception of gaze direction. First evidence came from electrophysiological studies by Perrett and coworkers. They found neurons in the macaque anterior and middle STS that responded selectively to different head orientations. A total of 64% of these neurons were sensitive to the eye-gaze direction as well (Perrett, Hietanen, Oram, & Benson, 1992; Perrett et al., 1985). A lesion study in macaques showed that after bilateral removal of the banks and floor of the anterior and middle part of the STS, monkeys were impaired in their ability to discriminate

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between different angles of eye gaze (Campbell, Heywood, Cowey, Regard, & Landis, 1990). In short, these studies strongly suggest the existence of a neural system in the anterior and middle part of the monkey STS dedicated to processing gaze direction (Langton, Watt, & Bruce, 2000).

More recently, neuroimaging studies have attempted to identify the substrates underlying the perception of eye gaze in humans. An early positron emission tomography (PET) study suggested that during processing of direct or averted gaze, several brain regions are specifically activated, including parts of the middle temporal gyrus (MTG) (Wicker, Michel, Henaff, & Decety, 1998). Functional magnetic resonance imaging (fMRI) work showed that the posterior part of the STS (pSTS) is involved in the perception of faces in which the eyes or mouth are moving, but not in the perception of other moving stimuli (Puce, Allison, Bentin, Gore, & McCarthy, 1998). Hoffman and Haxby (2000) also reported that eye-gaze perception elicits blood oxygen level-dependent (BOLD) activity in the pSTS, but in addition also in the intraparietal sulcus (IPS), the latter probably related to the encoding of the spatial direction of the perceived gaze (see below) (Pelphrey, Singerman, Allison, & McCarthy, 2003; Hoffman & Haxby, 2000). Hooker et al. (2003) extended the knowledge about the role of the pSTS by showing that the activation of this region is specific to the extraction of directional information from the eyes relative to directional information from an arrow and relative to eye motion without relevant directional information (moving inward toward the nose).

In summary, previous work suggests that the STS region (i.e., the cortex within the STS, the adjacent cortex on the surface of the superior temporal gyrus [STG] and MTG [near the straight segment of the STS], and the adjacent cortex on the surface of the angular gyrus [near the ascending limb of the STS]; Allison, Puce, & McCarthy, 2000) is involved in analyzing gaze cues that provide socially meaningful directional information. The work of Pelphrey, Singerman, et al. (2003) demonstrated that the STS region is as well sensitive to the social context within which a gaze shift occurs. In this fMRI study, subjects viewed an animated face which eye gaze shifted toward one of six locations. On "correct" trials, the eye gaze was directed at the location 1 to 3 sec before a small checkerboard appeared, on "incorrect" trials, the animated face shifted its gaze toward empty space. When subjects perceived gaze shifts inconsistent with their expectation ("incorrect" trials compared to "correct" trials), extended activation was observed in the STS region.

Besides the STS region, two recent PET studies have also implicated the amygdala and, possibly, the orbitofrontal cortex in gaze processing (Wicker, Perrett, Baron-Cohen, & Decety, 2003; Kawashima et al., 1999). The latter two regions are suggested to be especially in-

volved in the subsequent analysis of the emotional relevance of a stimulus (Allison et al., 2000; Emery, 2000).

Despite the consistency of the results, previous neuroimaging work on gaze direction has been suffering from two experimental limitations: (1) The demands on the processing of gaze direction have typically been very low, well below the demands on gaze processing characterizing the natural viewing as in most studies conducted so far, subjects perceived eyes moving to the left and right or up and down. Hence, gaze direction stimuli more akin to the natural situation may actually activate additional or even different substrates. (2) In all previous studies, subjects were not actively following the gaze of another person, but only passively observing shifts in eye gaze. Again, this is a configuration differing from the one prevailing under natural viewing conditions, with similar implications for the distribution of activation as discussed previously.

The first aim of our study was therefore to investigate whether gaze processing, probed with more demanding gaze shifts and, moreover, leading to gaze following of the observer leads to different patterns of activation. Besides the STS region, certainly a prime region of interest (ROI) in view of the work described, we were specifically interested in the IPS, as in several previous imaging studies, additional activation had been seen within this sulcus during the passive perception of gaze shifts (Pelphrey, Singerman, et al., 2003; Hoffman & Haxby, 2000; Puce et al., 1998; Wicker et al., 1998). As pointed out earlier, gaze shifts of another person are potent cues for shifting one's own spatial attention in the same direction (Driver et al., 1999). Accordingly, the gaze-related activity in the IPS has been interpreted as reflecting the involvement of the attentional system in encoding the spatial direction of another person's gaze and/or covert, reflexive shift of attention made by the subjects. However, the activity might just as well reflect the extraction of gaze direction or more complex interactions between visual processing and the reallocation of attention. In this case, the activity should be influenced by the properties of the cue guiding attention. However, previous work has not addressed the question if the IPS activation is the same for nonbiological and for eye-gaze cues providing spatial information. The second aim of our study, therefore, was to disentangle the roles of visual processing and attention shifting by comparing the BOLD response in the IPS when subjects used a perceived shift in eye gaze or a nondirectional symbolic cue to shift their spatial attention (details below).

In our study, subjects had to follow the directional cue provided by the eyes of another person toward an object in space (and establish joint attention). In order to do so, they had to detect the gaze direction of the eyes of a face presented on a screen, with high precision. Then they had to use this information to make a

saccade to one out of five possible targets (Condition 1: gaze following). The saccade targets where five pins with different shades of gray presented on the lower border of the stimulus image. Not only was the direction of the eye gaze shifting but the luminance of the two irises, which were in any case gray, was also changing, each adopting the gray level of one of the targets. In the control condition, subjects were instructed to use the changing iris gray value as a cue toward the correct target and ignore the shifts in eye gaze (Condition 2: gray value matching). In both conditions, exactly the same physical stimuli were presented. This means that during both conditions subjects perceived gaze shifts and changes in iris gray value. However, depending on the instruction, either the gray value or the direction cue was used to redirect gaze. In other words, we compared two conditions that were physically identical but differed cognitively.

In both conditions, not only was the gaze direction changing but also the appearance of the iris. This might have appeared unnatural and therefore could have influenced the activation pattern we found during gaze following. To check for this possible influence of iris gray level changes, we carried out a control experiment in which we compared the gaze following condition from the first experiment (with gray irises and changing iris gray levels) with a gaze following condition in which the portrayed person was shown with his natural iris gray level, which, moreover, was kept constant throughout the experiment.

METHODS

Subjects

Fifteen right-handed healthy adults (6 women, 9 men), age range 19–55 years (mean 26 years), participated in this study, which was approved by the Ethics Review Board of the Tübingen Medical School. All participants had normal or corrected-to-normal vision. Each subject provided written informed consent and was compensated for participating.

Experimental Stimuli

To create the experimental stimuli, photographs were taken from a head-fixed male person in front of a uniform black background using a digital camera at a distance of 150 cm (Nikon Coolpix 4500, Nikon, Japan). The person was looking into six possible directions: directly into the camera or to one of five target locations arranged on a horizontal board in the frontoparallel plane (at a distance of 30 cm from the viewer). The visual angle between the targets was 12.5°. The photographs were manipulated using Adobe Photoshop 7.0. The irises of the eyes were given five different gray

values, corresponding with the gray values of the five targets (see Figure 1).

Experimental Task and Procedure

During the fMRI scanning procedure, subjects lay supine in the MR-scanner, their head being secured by foam rubber to minimize head movements. Stimuli were presented on a translucent screen viewed by the subjects via a two-mirror system. A total of 40 stimuli (20 gaze following, 20 gray level matching) were presented in a pseudorandomized order arranged in four blocks per scanning session. Each block started with a visual instruction, followed by a picture of the five targets on the bottom and the human face looking straight ahead (see Figure 1). Subjects were instructed to fixate in between the eyes of the face (baseline condition). After 6–10 sec the next picture appeared containing the same targets and face but now with a different iris gray level and eyes gazing at one of the five targets. During the gaze following blocks (Condition 1) subjects had to follow the eye gaze toward the correct target and ignore the changing iris gray level. During the gray level matching blocks (Condition 2), subjects had to ignore the shift in eye gaze and move their eyes to the target whose gray value corresponded to that of the iris. Subjects were instructed to fixate on the chosen target for 3 sec until the "baseline picture" appeared again. The distance between the eyes of the subject and the stimulus screen was 150 cm. At this distance, the visual angle between the targets was 2.7°. The two tasks were exercised in a training session prior to the fMRI experiment. At the end of the training
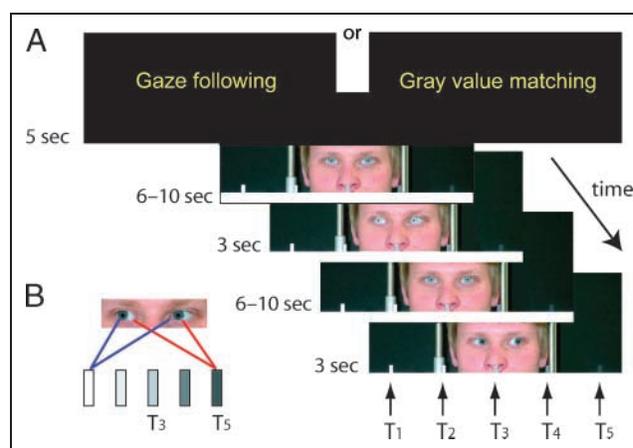
Figure 1. (A) Example of the pictures presented in both conditions: gaze following and gray value matching. The numbers indicate how long each picture is presented. T1–5 = target 1–5. (B) Schematic illustration of the stimulus. The eyes are directed at Target 1 (blue lines) and the iris gray value corresponds to Target 5 (red lines). In the gaze following condition, the subject should make a saccade toward Target 1, and in the gray value matching condition, the subject should make a saccade toward Target 5.

session and just before the start of the fMRI experiment, subjects performed a test session of 10 min. The total scanning time was approximately 40 min.

Eye Movement Tracking

During the test session at the end of the training, we recorded the subjects' horizontal and vertical eye movements, using a homemade iris-fit-eye-tracking system (operating at a spatial resolution of <1° and a temporal resolution of 20 msec). During the fMRI experiments, eye movements were controlled using a commercial infrared limbus-eye-tracking system (Cambridge Research Systems). A plastic cantilever attached to the head coil and the eyepiece of the tracking device allowed an individual adjustment. The limbus-eye-tracking system also provided a spatial resolution of <1° and a temporal resolution of 20 msec in optimal cases. However, in most (12 out of 15 subjects) of the subjects, the eye movement data were of much poorer quality, probably because of slight head movements made by the subject. Furthermore, although the limbus-eye-tracking system uses the limbus (the boundary between the white sclera and the dark iris), vertical eye movements were difficult to detect due to the occasional covering of the top and bottom of the limbus by the eyelids. These eye-tracking limitations precluded a quantitative analysis of eye movement behavior inside the scanner.

For those subjects for whom eye movement data were available for both situations, in the scanner and during the test session, the behavioral data did not show a qualitative difference. Furthermore, all subjects were very well trained before they went into the scanner. Therefore, we used the eye-tracking data acquired during the test session for behavioral analysis and the eye-tracking data acquired during the fMRI experiment as a control to see whether the subjects performed the two tasks of the experiment.

All the acquired eye-tracking data were analyzed using LabVIEW (National Instruments) and Matlab 6.5 (The MathWorks).

Imaging

Images were acquired using a 1.5-T MR Scanner (Magnetom Sonata Maestro Class; Siemens, Erlangen, Germany). Functional scans consisted of T2*-weighted echo-planar image volumes (TE 40 msec, TR 3000 msec, flip angle 90°) covering the whole brain (36 transverse slices, matrix 64 × 64, slice thickness 3.2 mm + 0.8 mm gap, in-plane resolution 3 × 3 mm). The experiment contained three sessions, in which a total of 492 volumes were taken.

After the functional scans, a T1-weighted structural MRI was obtained for each subject using a magnetization-prepared, rapid acquisition gradient-echo (MP-RAGE) sequence (TE 3.87 msec, TR 1900 msec, TI 1100 msec, flip angle 15°, 176 × 256 × 256 voxel, voxel size 1.0 × 1.0 × 1.0 mm^3).

Image Preprocessing

Images of each subject were preprocessed using the statistical parametric mapping program package SPM2 (Wellcome Department of Cognitive Neurology, London, UK, www.fil.ion.ucl.ac.uk/spm) to permit application of random field theory for statistical inference. Functional images were first spatially realigned and slice time corrected. Structural images were coregistered to the mean volume of the functional images and normalized into Montreal Neurological Institute (MNI) space (Friston et al., 1995). The calculated nonlinear transformation was applied to all functional images. Normalized data were then spatially smoothed using a Gaussian filter (10 mm full width half maximum). Finally, the time series in each voxel were high-pass-filtered with a cutoff frequency of 1/128 Hz.

Analysis of MRI Data

Data analysis was performed by modeling the events of the two tasks (gaze following and gray level matching) with a canonical hemodynamic response function and applying the general linear model. The change of the eye gaze and the iris gray level was used as the onset time points of the events. Regressors representing estimated head movements (translation and rotation with six degrees of freedom) were added into the model as covariates of no interest to account for artifacts due to head movements during scanning. Contrasts for the gaze following and gray level matching condition versus rest (baseline) as well as a subtraction analysis of both conditions were calculated for each subject. Significant changes were assessed using t statistics. For the group analysis, single-subject contrast images were analyzed at a second level using a random effects model, comparing the average activation for a given voxel with the variability of that activation over the examined population (Friston, Holmes, & Worsley, 1999). To exclude the possibility that deactivations were responsible for our results, we considered only those voxels in the random effects model, which had exhibited significant ($p \leq .05$, uncorrected) activations in the gaze versus rest and gray level versus rest contrasts, respectively. Activation is reported if statistical significance exceeded $p < .001$ (uncorrected) on the single voxel level and, furthermore, activation in at least 10 neighboring voxels exceeded this level. We visualized these activations on a SPM2 template brain or on a SPM2 average coregistered T1 image.

To compare the clusters of activation we found in our study with previous studies on eye-gaze processing, we projected the centers of the clusters of our study and of seven previous studies on a population-average

fiducial brain surface (PALS-B12 atlas) (http://brainmap.wustl.edu:8081/sums/directory.do?id=636032) available on the Caret Website (http://brainmap.wustl.edu/caret) (Van Essen, 2002; Van Essen et al., 2001).

The percent signal change of the BOLD signal during both conditions compared to the rest condition was calculated in four ROIs using the ROI toolbox MarsBaR (Brett, Anton, Valabregue, & Poline, 2002). The ROIs were defined based on the clusters of activation found during both tasks versus the rest condition and therefore independent of the difference in activation between the two tasks. The center of the STS ROIs were located at Talairach coordinates (Talairach & Tournoux, 1988): $x = 47, y = -67, z = 9$ (right STS) and $x = -50, y = -61, z = 9$ (left STS). The ROIs ranged from $x = 42$ to 52, $y = -70$ to $-64, z = 4$ to 14 (right STS) and $x = -54$ to $-46, y = -64$ to $-58, z = 6$ to 12 (left STS). The center of the IPS ROIs were located at Talairach coordinates $x = 32, y = -49, z = 51$ (right IPS) and $x = -28, y = -52, z = 53$ (left IPS). The ROIs ranged from $x = 12$ to 55, $y = -76$ to $-22, z = 43$ to 66 (right IPS) and $x = -44$ to $-12, y = -74$ to $-24, z = 42$ to 66 (left IPS). The mean of the percent signal change was calculated for each region, averaging across voxels and across repetitions of blocks, in each subject. A Wilcoxon test was used to compare the percent signal change between the two conditions.

RESULTS

Behavioral Performance

There was neither a difference in the accuracy ($p = .78$) nor in the response times ($p = .06$) between the two conditions: gaze following [correct answers: mean = 80.9%, SEM = 2.8%; reaction times (time between go signal = change of gaze/gray level and onset of eye movement defined by a velocity threshold): mean = 784 msec, SEM = 57 msec] and gray level matching [correct answers: mean = 79.9%, SEM = 2.0%; reaction times: mean = 826 msec, SEM = 64 msec] (Figure 2). This indicates that the two conditions were equal in difficulty and attentional load.

fMRI Responses

The brain activation patterns provided by the gaze minus rest contrast and the gray level minus rest contrast, respectively, were very similar (Figure 3A and B). During both conditions, a number of brain regions were activated (i.e., they had a significantly higher BOLD signal compared to the rest condition), including the frontal eye field (FEF), the supplementary eye field (SEF), the dorsolateral prefrontal cortex (DLPFC), the premotor cortex, the IPS, the fusiform gyrus (FG), the occipito-temporal cortex, as well as the superior colliculus (SC) (the latter not shown), all bilateral. More

Figure 2. Behavioral data for the gaze following (black bars) and gray value matching (white bars) condition. (A) Percentage of correct answers. (B) Reaction times (msec).

interesting is the difference between both conditions because this reveals which brain regions are specifically activated when we detect and use a directional cue from the eyes (gaze following) as opposed to detecting and using a symbolic cue from the eyes (gray level matching) to redirect our own gaze. Subtracting gray level matching related activation from gaze following related activation revealed that the posterior part of the middle temporal gyrus (pMTG) bilaterally and the cuneus were more activated during the gaze following condition compared to the gray level matching condition. The cluster within the MTG is located in a region termed the ''STS region'' by Allison et al. (2000) (see Introduction) (Figure 3C) and will be referred to as the pSTS region as it is located in the more posterior parts of the STS region. We did not find any brain region that was more activated in the gray level matching condition compared to the gaze following condition (Figure 3D). Note that the strong activation observed in the occipital, parietal, and premotor cortices in both tasks was completely cancelled out in the subtraction analysis, with the exception of the activation in the STS region and the cuneus in the gaze following condition.

Because we were especially interested in the STS region and the IPS (see Introduction), we performed an ROI analysis for these two regions to further quantify the activation we found in the whole-brain analysis. Figure 4 shows the average percent signal change for each region calculated across subjects. The difference in the percent signal change between the gaze following task and the gray level matching task was significant for the right ($p < .001$) and left ($p < .001$) STS

Figure 3. Group data showing the activation patterns for (A) the gaze–rest contrast; (B) the gray value–rest contrast; (C) the gaze–gray value contrast; and (D) the gray value–gaze contrast superimposed on an SPM brain template (A, B, D: lateral view, C: lateral and dorsal view, $p < .001$, uncorrected). R = right hemisphere; L = left hemisphere; DLPFC = dorsolateral prefrontal cortex; FEF = frontal eye field; IPS = intraparietal sulcus; MT/V5+ = medial temporal area; pMTG = posterior middle temporal gyrus; STS = superior temporal sulcus.
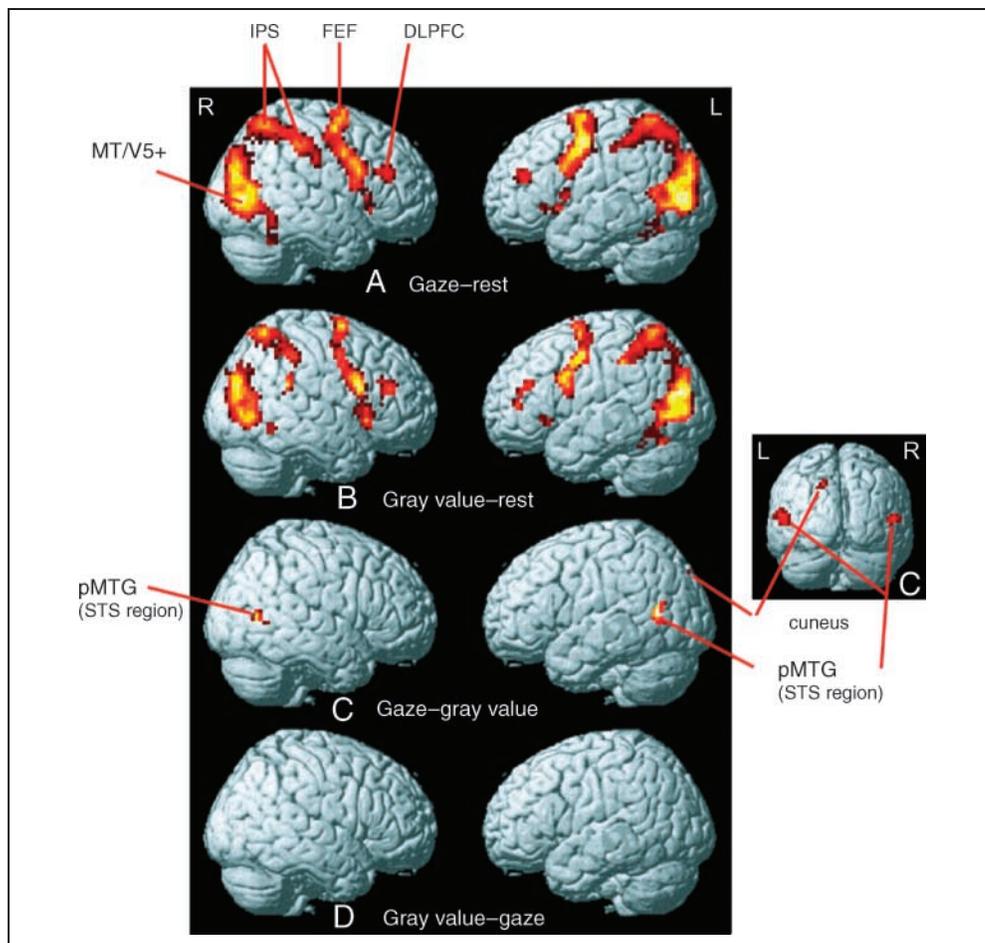
region. No significant difference was found between both conditions for the right ($p = .97$) and left ($p = .57$) IPS. This ROI analysis confirms the pattern of activity observed in the whole-brain contrasts.
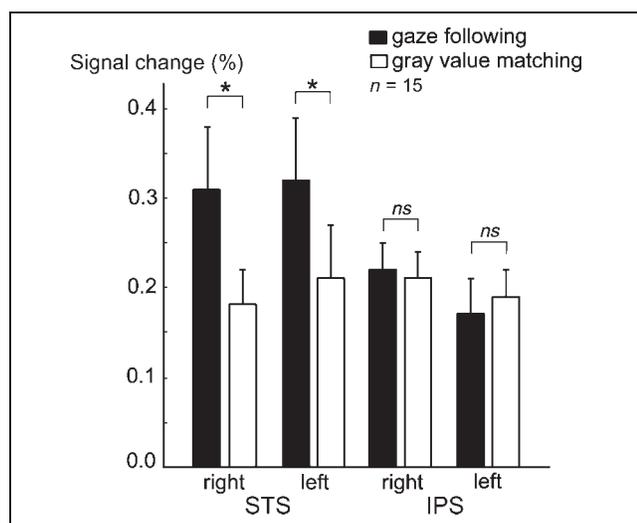
Figure 4. Average BOLD signal change ($n = 15$) from the ROIs defined in the right and left STS region and the right and left IPS. The black bars represent the gaze following condition, the white bars represent the gray value matching condition.

In our control experiment in which we compared the gaze following condition from the first experiment (with artificially changing iris gray level) with a gaze following condition in which the iris gray level was not changing (natural iris gray level), we found that the right inferior occipital gyrus (IOG) was more activated when subjects followed the eye gaze of a person with artificially gray shaded eyes compared with natural colored eyes (Figure 5). For the opposite contrast (natural colored eyes minus artificially colored eyes), we found no significant brain activation.

To compare the activation we observed in the STS region with previous studies on eye-gaze processing, we projected the center of activation within the STS region of seven previous studies and our study (red symbol) on a population-average fiducial brain surface (see Methods) (Figure 6). The coordinates of the activation centroids are given in Table 1. In all previous studies, activation was found within the posterior part of the right STS region, with the location of our right MTG activation fitting within the range of those previous activations. In four of the seven previous studies, activation was reported in the posterior part of the left STS region, again at a location similar to the one observed by us. Some of the activation centroids seem to be located outside the brain surface. This is due to the fact that for
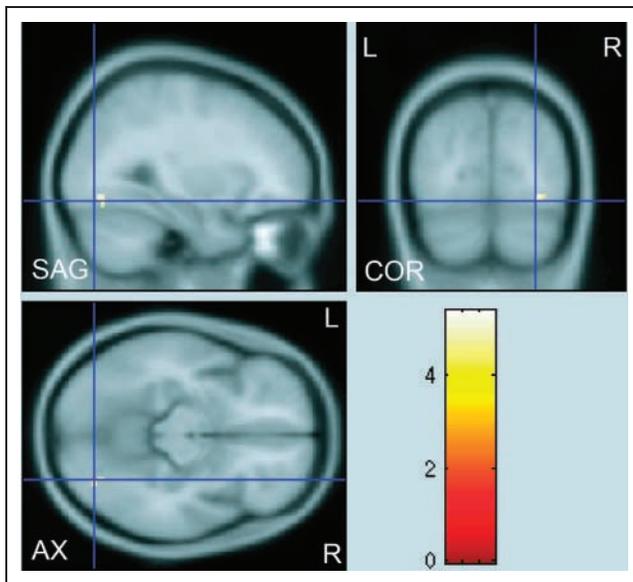
Figure 5. Brain activation for the unnatural–natural colored eyes contrast superimposed on an average T1 template image (sagittal [sag], coronal [cor] and axial [ax] view, $p < .001$ uncorrected) ($n = 10$). R = right hemisphere; L = left hemisphere. Activation was found in the inferior occipital gyrus (IOG); Talairach coordinates (31, −75, −5).

the generation of the surface a segmentation boundary is used that runs approximately midway through the cortical gray matter (cortical layer 4) (Van Essen, 2005). All of the activation centroids, except those from Puce et al. (1998), thus seem to be located in the outer cortical layers.

DISCUSSION

The present study confirms and extends our knowledge about the neuronal correlates of gaze following and joint attention. In our study, subjects had to use two different types of cues to reorient their attention to a target in space. The first cue was a socially relevant directional cue (eye-gaze direction: gaze following condition), the
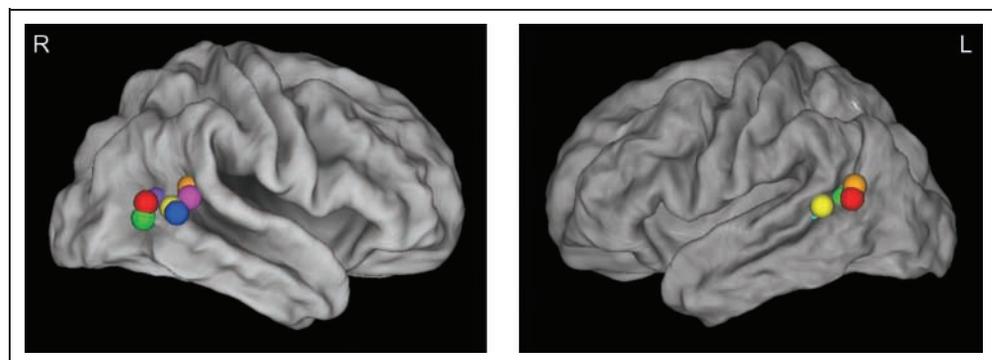
second cue was a nonsocial symbolic cue (iris gray value: gray level matching condition). Comparing the BOLD signal elicited by the use of these two cueing types revealed that the pSTS region and the cuneus are involved in extracting and using detailed directional information from the eyes of another person to redirect one's own gaze and establish joint attention.

Oculomotor Control

In both the gaze following and gray level matching condition, independent of which cue was used, activations were found in a well-known cortical network underlying the generation of saccades. Specifically, responses were found in the FEF, the SEF, the IPS, and the SC, all known to be involved in the control of goal-directed saccades. The activation in the FEF extended ventrally along the precentral gyrus into an area referred to as the ventrolateral premotor cortex (PMC). Several imaging studies have reported activation in the ventrolateral PMC during the generation of different types of saccadic eye movements (Konen, Kleiser, Wittsack, Bremmer, & Seitz, 2004; Heide et al., 2001; Nobre, Gitelman, Dias, & Mesulam, 2000; Petit, Clark, Ingeholm, & Haxby, 1997). Bilateral activation was also found in the DLPFC, known to be involved in the preparation of saccades and recently shown to be specifically involved in directional decisions about forthcoming intentional saccades (Milea, Lobel, Lehéricy, Pierrot-Deseilligny, & Berthoz, 2005). In our study, subjects also had to decide about the directions of a forthcoming saccade, here based on information coming from the eyes of another person.

STS Region

Compared with using a nonsocial symbolic cue (iris gray value), using a socially relevant directional cue (eye-gaze direction) to reorient attention was associated with highly specific bilateral activations in the pSTS region. This finding cannot be explained by differences in difficulty or attentional load between the gaze

Figure 6. Center of activation from the current study and prior neuroimaging studies (Table 1) of perceived eye movements, projected onto a population-average fiducial brain surface (PALS-B12 atlas; see Methods). R = right hemisphere; L = left hemisphere.

Table 1. Center of Activation from the Current Study and Prior Neuroimaging Studies of Perceived Eye Movements in the STS Region

Study	Symbol	Location	Side	BA	Talairach Coordinates (x, y, z)		
Wicker et al. (1998)	●	MTG	R	21	62	−50	06
Puce et al. (1998)	●	STS	R	22	47	−53	07[a]
		STS	R	22	49	−49	03[a]
		MTG	L	21	−49	−48	03
		MTG	L	39	−46	−53	05[a]
Hoffman and Haxby (2000)	●	MTG	R	37	50	−63	04
		MTG	L	39	−45	−56	11
Dubeau et al. (2002)	●	MTG	R	21	58	−52	08
		STS	L	22	−56	−48	08
Hooker et al. (2003)	●	STS	R	22	50	−45	16
		STS	L	19	−49	−61	16
Pelphrey et al. (2004)	●	STS	R	22	55	−45	12
Pelphrey, Morris, Michelich, et al. (2005)	●	MTG	R	22	46	−58	11
Current study	●	MTG	R	37	52	−62	10
		MTG	L	37	−52	−60	11

BA = Brodmann's area; STS = superior temporal sulcus; MTG = middle temporal gyrus.

[a]Not visible in Figure 6.

following and gray level matching task because the behavioral results showed that both tasks were equally demanding.

The STS region is known to be involved in passive viewing of moving eyes (Pelphrey, Morris, Michelich, Allison, & McCarthy, 2005; Pelphrey, Viola, & McCarthy, 2004; Hooker et al., 2003; Dubeau, Iacoboni, Koski, Markovac, & Mazziotta, 2002; Hoffman & Haxby, 2000; Puce et al., 1998; Wicker et al., 1998). During both the gaze following and gray level matching task of our study, the same stimuli were presented. Consequently, subjects perceived during both tasks shifts in eye gaze and changes in iris gray value, only the cue that they used to reorient their attention was different. Therefore, we can conclude that the pSTS region is not only involved in the passive observation of moving eyes but also in extracting and using detailed directional information from the eyes of another person to redirect one's own gaze. The ROI analysis we performed in the pSTS region confirmed the finding of the voxel-based group analysis. In both the right and the left pSTS region, we found significantly higher activation when subjects used eye-gaze direction compared to iris gray value as a cue to reorient their attention. During the gray level matching task, subjects still passively perceived shifts in eye gaze, which may explain the residual activation observed in the pSTS region during this condition.

During the gaze following task, aside from the changing gaze direction, the gray level of the iris changed between different shades of gray. This might have looked unnatural, and therefore, might have influenced the activation pattern we observed during the gaze following task. To examine this possible influence, we performed a control experiment in which, during the gaze following task, the iris gray level was changing only half of the time. During the other half of the time, the iris gray level stayed natural. Comparing the brain activation pattern during gaze following of artificially gray leveled eyes versus natural gray leveled eyes revealed a region in the right IOG that was more activated when the iris gray level was artificially changing. The IOG has recently been shown to be sensitive to the physical aspects rather than the identity of a face (Rotshtein, Henson, Treves, Driver, & Dolan, 2005). In our task, only one physical aspect of the face was changing (iris gray level), and not the identity of the face. Importantly, no influence of the artificially changing iris gray level was observed in the pSTS region or the cuneus during the gaze following task.

Cuneus

Besides the pSTS region, we observed a small cluster on the border between the cuneus and the precuneus that

was more activated in the gaze following condition compared to the gray level matching condition. (Pre)-cuneus activation has been reported in previous imaging studies on "theory of mind" (Völlm et al., 2006; Farrow et al., 2001), facial expression processing (Kilts, Egan, Gideon, Ely, & Hoffman, 2003), and social interaction (Schilbach et al., 2006). In the latter study, extensive precuneus activation was found when subjects observed a virtual character looking at (an imagined) other person compared to looking at the subject himself (thus observing averted versus direct gaze). In our gaze following condition, subjects were also socially interacting with the person they observed on the stimulus picture by using directional information from the averted gaze of this person to detect where he was looking at and establish joint attention.

Interestingly, cortico-cortical connections are found between the precuneus and the dorsal bank of the caudal part of the STS in capuchin and macaque monkeys (Leichnetz, 2001). Little is known about the functional connection of the (pre)cuneus and STS, but because the (pre)cuneus also appears to play an important role in assigning first-person perspective and possible also in shifting between first- and third-person perspective (Cavanna & Trimble, 2006), this might explain the involvement of the (pre)cuneus in triadic gaze processes such as joint attention. In summary, besides the pSTS region, the (pre)cuneus also seems to play a role in social interaction and gaze processing.

The finding that the pSTS region is specifically involved in joint attention is important for research on autism, which has considered that disturbed gaze processing might contribute to the autistic phenotype (Baron-Cohen et al., 1996). People with autism spectrum disorders are not impaired on the most basic aspects of gaze perception because they can distinguish between directed and averted eye gaze (Baron-Cohen et al., 1995). However, they have difficulties in more challenging aspects of gaze processing, needed for joint attention (Leekam et al., 1998, 2000) and, ultimately, for the formation of a "theory of mind" (Baron-Cohen et al., 1995). Joint attention is of particular interest because it is one of the most reliably identified early abnormalities in children with autism (Charman, 2003; Baron-Cohen et al., 1996). Several brain structures have been suggested to be affected or functionally impaired in people with autism spectrum disorders, including the amygdala (Baron-Cohen et al., 1999; Bauman & Kemper, 1985), the cerebellum (Boddaert et al., 2004; Fatemi et al., 2002; Ritvo et al., 1986), the frontal lobe (Courchesne & Pierce, 2005; Levitt et al., 2003), the parietal lobe (Courchesne, Press, & Yeung-Courchesne, 1993), and the STS region (Boddaert et al., 2004; Levitt et al., 2003). Because in our study, from those regions, only the STS region was found to be specifically involved in establishing joint attention, we suggest that impaired functioning of this brain region might underlie the joint attention

deficit in individuals with autism. This is in agreement with Dakin and Frith (2005), who suggested that abnormalities in the STS might provide a neural basis for the range of motion-processing deficits observed in autism spectrum disorder, including disturbances of biological motion perception. There is mounting functional imaging evidence that the pSTS is specifically activated during the perception of several forms of biological motion, such as moving point-light figures (Beauchamp, Lee, Haxby, & Martin, 2003; Grossman et al., 2000), moving body parts (Pelphrey, Morris, Michelich, et al., 2005; Pelphrey et al., 2004; Hooker et al., 2003; Dubeau et al., 2002; Hoffman & Haxby, 2000; Puce et al., 1998; Wicker et al., 1998), or whole body movement (Beauchamp et al., 2003; Pelphrey, Mitchell, et al., 2003), which is recently extended by the finding that repetitive transcranial magnetic stimulation (rTMS) over the pSTS temporarily impairs the perception of biological motion in healthy human subjects (Grossman, Battelli, & Pascual-Leone, 2005). Recently, an fMRI study showed that in participants with autism, the pSTS region is not sensitive to intentions conveyed by the observation of gaze shifts. In this study, subjects passively observed a virtual character shifting gaze to one out of six possible locations 1 sec after the appearance of a checkerboard in the character's field of view. In the congruent trials, the character shifted gaze toward the checkerboard, confirming the subject's expectation. In the incongruent trials, the character shifted gaze toward empty space, violating the subject's expectation. In both participants with autism and healthy controls, activation was found in the pSTS region when observing gaze shifts. However, only in healthy subjects was a difference found between congruent and incongruent shifts of gaze (Pelphrey, Morris, & McCarthy, 2005). This indicates that, in contrast to healthy controls, in individuals with autism the activity in the pSTS region is not modulated by the context of the perceived eye gaze. In summary, the pSTS region seems to be involved in both the basic aspects of gaze processing, such as passively observing gaze shifts, and in more demanding aspects of gaze processing, such as establishing joint attention or reading intentions conveyed by shifts in eye gaze.

IPS Region

Besides the STS region, previous imaging studies identified a region within the IPS involved in the passive observation of gaze shifts (Pelphrey, Singerman, et al., 2003; Hoffman & Haxby, 2000; Puce et al., 1998; Wicker et al., 1998). This gaze-related activity in the IPS has been interpreted as reflecting the involvement of the attentional system in encoding the spatial direction of another person's gaze. However, whether the role played by the IPS in mediating shifts of spatial attention is the same when this shift is elicited by a perceived eye gaze or by a nondirectional cue is not known and could not

be tested in those previous studies. In our study, we could directly address this question because subjects had to shift their spatial attention based on a perceived shift in eye gaze in the gaze following task or based on a nondirectional symbolic cue in the gray level matching task. During both tasks, strong activation was found within the whole IPS region, ranging from the posterior parietal cortex to the postcentral sulcus. However, in contrast to the clear difference in activation pattern we found in the pSTS region between both tasks, no difference was observed in the IPS. This finding was confirmed by the ROI analysis we performed in the IPS, which revealed no significant difference between the change in BOLD signal elicited by the use of eye-gaze information compared to the use of a nondirectional symbolic cue to reorient spatial attention. We conclude that the IPS is involved in encoding spatial direction and mediating shifts of spatial attention independent of the type of cue that triggers this process.

Conclusion

In this study, we showed that the pSTS region and the cuneus, and not the IPS, are specifically involved in extracting gaze direction in order to establish joint attention. This finding extends our knowledge about the pSTS region being involved in the passive observation of shifts in eye gaze and is in accordance with the finding that activation in the pSTS region is sensitive to the social context within which a gaze shift occurs. The pSTS region thus plays an important role in various stages of gaze processing. To ascertain the role of the cuneus in gaze processing and the functional connectivity between the pSTS region and the cuneus, further experiments are needed.

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