

Differential activation of frontoparietal attention networks by social and symbolic spatial cues

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Perception of both gaze-direction and symbolic directional cues (e.g. arrows) orient an observer's attention toward the indicated location. It is unclear, however, whether these similar behavioral effects are examples of the same attentional phenomenon and, therefore, subserved by the same neural substrate. It has been proposed that gaze, given its evolutionary significance, constitutes a 'special' category of spatial cue. As such, it is predicted that the neural systems supporting spatial reorienting will be different for gaze than for non-biological symbols. We tested this prediction using functional magnetic resonance imaging to measure the brain's response during target localization in which laterally presented targets were preceded by uninformative gaze or arrow cues. Reaction times were faster during valid than invalid trials for both arrow and gaze cues. However, differential patterns of activity were evoked in the brain. Trials including invalid rather than valid arrow cues resulted in a stronger hemodynamic response in the ventral attention network. No such difference was seen during trials including valid and invalid gaze cues. This differential engagement of the ventral reorienting network is consistent with the notion that the facilitation of target detection by gaze cues and arrow cues is subserved by different neural substrates.

Keywords: arrow; eyes; fMRI; gaze

INTRODUCTION

Perceiving another person's gaze-direction rapidly orients one's own attention to the gazed-at location (Driver *et al.*, 1999; Langton and Bruce, 1999; Friesen and Kingstone, 1998). The neurophysiological mechanisms responsible for this rapid orienting response are currently unknown. Dual-process theories of attention (e.g. Egeth and Yantis 1997; Corbetta and Shulman 2002) distinguish between goal-driven (voluntary or orienting) and stimulus-driven (reflexive or reorienting) mechanisms of attention. In the goal-driven mode, high-level cognitive processes such as task goals determine where attention is to be allocated. In the stimulus-driven mode, stimuli that have high attention-grabbing power (typically, abrupt onsets or feature singletons) cause a reallocation or shift of attention to occur without conscious effort (Pashler and Harris, 2001). Is it the case that biologically salient directional cues such as averted eyes rely primarily on the same stimulus-driven reorienting system that is recruited by abrupt stimulus onsets?

Studies of attention orienting to gaze and arrow cues largely rely on a modified version of a paradigm developed by Posner and colleagues (1980), in which participants are asked to report the appearance of a target stimulus that appears at a location lateral to central fixation. Prior to the onset of this target, a centrally presented directional cue (e.g. an arrow) appears onscreen. In the valid condition this cue will accurately indicate the subsequent target location, whereas in the invalid condition the cue will indicate the 'wrong' location. A speeded response to a validly cued target is thought to indicate an allocation of attention (i.e. orienting) to the target's location prior to the target's onset. During invalid trials, the target's onset at the un-cued location results in a re-orienting of attention to the target.

Earlier studies suggested that eye gaze acts as a special attention cue that reflexively orients attention. Support for this notion came from studies showing that gaze-cued attention shared characteristics with reflexive attention. As with stimulus-driven reorienting, gaze cues trigger attentional shifts even when the time interval between the presentation of the cue and the target is short (around 100 ms; Langton and Bruce 1999; Ristic *et al.*, 2002; Friesen and Kingstone 2003). Unlike voluntary attention orienting (Müller and Rabbitt 1989), orienting to gaze cues is not susceptible to top down control (Driver *et al.*, 1999; Downing *et al.*, 2004; Friesen *et al.*, 2004; Ristic *et al.*, 2007). In addition to the behavioral evidence, the evolutionary and social significance

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of eye gaze (cf. Emery *et al.*, 2000) and the existence of ostensibly specialized temporoparietal brain networks for encoding gaze direction (Hoffman and Haxby 2000; Hooker *et al.*, 2003; Calder *et al.*, 2007) have also been taken to support reflexive orienting to gaze direction.

Contrary to the notion that gaze is a special attentional cue, many studies have since demonstrated that arrow cues evoke similar shifts of attention (e.g. Tipples, 2002; Ristic *et al.*, 2002). Arrow cues even demonstrate some of the resistance to top-down control that was initially attributed only to gaze cues (Tipples, 2008; Kuhn and Kingstone, 2009). This has led some to conclude that both cue types effectively and reflexively re-orient spatial attention, but that response to gaze cues is 'more reflexive' (Ristic *et al.*, 2007).

Imaging studies have shown that goal-driven orienting and stimulus-driven orienting are associated with partially separable networks in the brain. Goal-driven control of attention is associated with activation in the dorsal parietal and superior frontal cortices, whereas stimulus-driven control of attention is associated with activation in the temporoparietal and inferior frontal cortices (Corbetta *et al.*, 2000; Yantis *et al.*, 2002; Mayer *et al.*, 2004; Thiel *et al.*, 2004). Specifically, the dorsal attention system comprises the intraparietal sulcus (IPS) and frontal eye fields (FEF) bilaterally and is engaged during goal-driven shifts of attention. The ventral attention system comprises the right temporoparietal junction (TPJ) and right ventral frontal cortex (including the inferior frontal gyrus, middle frontal gyrus and anterior insula) and is engaged, along with the dorsal system, during stimulus-driven reorienting of attention (cf. Corbetta *et al.*, 2008). Attempts using functional magnetic resonance imaging (fMRI) to investigate the engagement of these attention systems in the brain during gaze and arrow-triggered orienting have yielded mixed results. Two studies reported activation of separate attention systems by gaze and symbolic directional cues (Kingstone *et al.*, 2004; Hietanen *et al.*, 2006) while two others have reported a common neural substrate (Tipper *et al.*, 2008; Sato *et al.*, 2009).

Kingstone and colleagues (2004) used a perceptually ambiguous cue that could either be perceived as a pair of eyes under a top hat or as a car. Reliable behavioral cuing effects were observed for both the eyes and car conditions. Activation in the right superior temporal sulcus (STS) was greater in the eyes than in the car condition, but this difference was not observed in the attention systems. However, STS activation is known to increase when participants attend to the eyes (gaze) *vs* identity of a face (Hoffman and Haxby, 2000). Therefore, the observed STS response could result from the changed percept (eyes *vs* car) of the stimulus and not necessarily from attention orienting.

Tipper and colleagues (2008) used a similar design using fixed-effects fMRI data analysis and came to a different conclusion. Triangular cues that could be perceived as either a profile view of an eye or an arrow evoked a significant

response within occipital and frontal attention controlling areas when contrasted with a fixation baseline. These areas comprise components of both the dorsal (e.g. right IPL) and ventral (e.g. right TPJ) attention systems. When contrasted directly, cues perceived as gaze evoked a stronger than cues perceived as arrows response in a small subset of these regions, including ventral frontal areas that are part of the ventral attention network. The authors thus concluded that attentional orienting by gaze and arrows share a common neural substrate that is more effectively engaged by gaze. An alternative interpretation is that highly schematized eyes, such as those used in the study, do not effectively engage the brain's gaze perception systems. It has been suggested that perception of gaze direction is a largely innate ability (Hood 1998) and, as such, would rely on stereotypical physical features of the eye. Indeed, the morphology of the human eye is distinct and, in many regards, unique among primates (Kobayashi and Kohshima 1997). Many, if not most, of these distinct characteristics are preserved even in simple line drawings (e.g. Friesen and Kingstone 2003; Hietanen *et al.*, 2006) but are absent from the stimuli used by Tipper and colleagues (2008). Though this might seem inconsistent with the effective behavioral cuing achieved in Tipper *et al.*'s study when the stimulus was perceived as an eye, an alternative explanation is that participants may have simply flipped their perception of what constituted the leading edge of the stimulus. That is, participants could have simply perceived the 'eye' stimulus as an abstract symbol pointing toward the opposite direction as the 'arrow' stimulus, thus speeding reaction times to valid targets without recruiting the neural system underlying gaze perception.

Hietanen and colleagues (2006) and Sato and colleagues (2009) both investigated directional *vs* non-directional gaze and arrow cues by contrasting directional cues with a direct gaze (in the gaze condition) or a non-directional shape (in the arrow condition). Hietanen *et al.* observed that orienting by arrows rather than gaze was more contingent on the voluntary (particularly the FEF) attention system. Sato *et al.* found directional *vs* nondirectional gaze cues resulted in no significant differences, whereas directional *vs* nondirectional arrow cues recruited the ITG/MTG and SPL. Contrary to the results of Kingstone *et al.* (2004) and Tipper *et al.* (2008), these studies suggest that arrow rather than gaze cues are more effective in recruiting the brain's attention systems. However, the validity of the aforementioned contrasts is predicated on the assumption that a direct gaze and a non-directional shape are equivalent baselines. This may not be the case, as direct gaze is known to capture or reorient attention (von Gröna and Anston 1995; Senju and Hasegawa 2005; Doi and Ueda 2007).

In sum, there is no conclusive neuroimaging evidence that the dorsal and ventral attention systems are differentially engaged by gaze and arrow cues. In the current study, we attempt to clarify whether gaze and arrow cues evoke similar or different activation patterns in these systems. Our study

involved three methodological advances over previous ones. First, to compare our findings directly with those obtained in previous neuroimaging studies on the goal-driven and stimulus-driven attention networks (Corbetta *et al.*, 2000; Yantis *et al.*, 2002; Mayer *et al.*, 2004; Thiel *et al.*, 2004), we assessed the reorienting effects by comparing invalidly cued trials with validly cued trials. We focused on the reorienting attention system because, as with gaze, non-predictive arrow cues result in orienting toward the cued location (e.g. Ristic *et al.*, 2002; Tipples, 2002). Therefore, contrasting invalid and valid trials will reveal any differences in reorienting attention to the onset of the invalidly cued target. Moreover, this approach avoids the potential confounds of using a direct gaze cue as the baseline in our critical contrast and more directly assesses the reorienting response than has been done previously (cf. Hietanen *et al.*, 2006). Second, we used near photo-realistic computer-generated face images that are more ecologically valid than schematic gaze cues. Third, we used an event-related fMRI design and modeled the subjects as random effects, enabling us to draw inferences at the population level. As in most cueing studies, the participants were engaged in a detection task in which the target appeared to the left or right of fixation and was preceded by a non-predictive gaze or arrow cue.

As a secondary aim, we investigated whether direct gaze was an appropriate baseline for this type of experiment. Direct gaze can capture attention (von Grönau and Anston, 1995), whereas 'direct' arrows are non-directional and would therefore not be expected to engage attention control systems. Downward cues were included to address this potential baseline confound as they are equally informative directional cues for both gaze and arrows. We were then able to compare contrasts that used direct cue baselines with those using downward cue baselines.

MATERIALS AND METHODS

Subjects

Sixteen participants (12 women, mean age = 25.8 years, s.d. = 6.7) completed the fMRI study for payment. Participants were right-handed with normal or corrected vision. All participants gave informed consent prior to the experiment and were fully debriefed at its completion. A local ethics committee approved the study (LREC 07/Q0102/47).

Stimuli

Gaze stimuli were 20 near photo-realistic portraits of faces created using the FaceGen software package (Singular Inversions, Vancouver, BC). Each face was manipulated with FaceGen to appear in five eye gaze positions (eyes closed, direct gaze, downward gaze, left gaze and right gaze; Figure 1). Faces subtended a horizontal visual angle of 4.9° and were centered in the middle of the display. Arrow stimuli were bold white lines on a black background

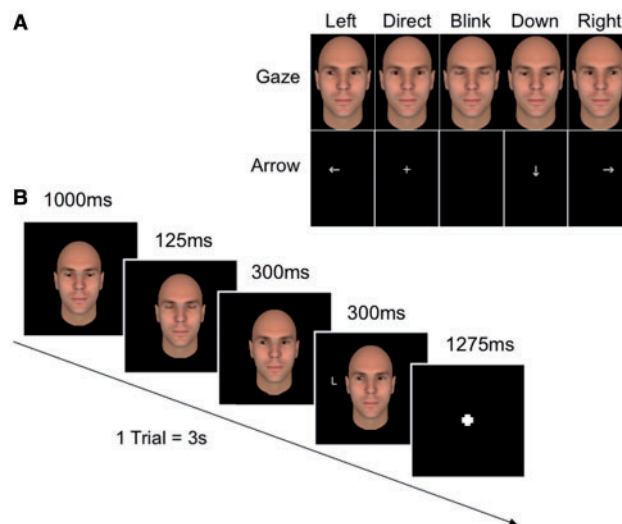


Fig. 1 (A) Example of gaze (top row) and arrow (bottom row) stimuli. From left to right: left, direct, blink, down, right. (B) Sample trial sequence with a gaze cue.

(Figure 1) created with Adobe PhotoShop CS (Adobe, CA). As with the gaze cues, the arrow condition cues could be nonexistent (cf. closed eyes), point down, to the left or right or none of these three directions (cf. direct gaze). Arrows subtended 0.7° and extended from the center of the display in the relevant direction. The arrows extended from the center of the display, rather than being centered in the display, in order to ensure that the arrowhead and the eye closest to the target were equidistant from the target in the valid cue condition. The target stimulus was a 0.35° high letter 'L' presented 3.8° to the left or right of the center of the display.

Task

Throughout all trials the participants were required to fixate a small cross presented at the center of the screen and monitor for the appearance of the letter 'L' to the left or right of the face or arrow display and, upon detection, report on which side the letter appeared as quickly as possible by pressing a button with their left or right index finger. A target localization task was used as opposed to simple target detection in an effort to maximize the behavioral effect (cf. Friesen and Kingstone 2003). Importantly, participants were explicitly informed that the centrally presented cues had no predictive value regarding the subsequent target location.

A single gaze cuing trial would begin with a 1000 ms presentation of a face with gaze averted downward. The image was presented on the screen for 1000 ms in order to minimize any directional cueing effect of the image. This display was followed immediately with a 125 ms presentation of the same face with closed eyes. Following this 'blink', the cue display (face with eyes averted downward, direct, left or right) appeared. After 300 ms, the target appeared, thus

resulting in a 300 ms stimulus-onset asynchrony (SOA). A 300 ms SOA has previously been used to successfully elicit the cuing effect for both gaze and arrows (e.g. Friesen and Kingstone 2003; Driver *et al.*, 1999; Friesen *et al.*, 2004; Langdon and Smith, 2005; Sato *et al.*, 2009). Participants were instructed to report as quickly and accurately as possible on which side the 'L' appeared via a button press. After 300 ms both the face and target-letter would be replaced by a fixation cross that would remain on the screen for the 1275 ms remainder of the trial. The arrow trials were similar to the gaze trials with the exception that respective arrow cues were displayed, and the initial 1000 ms presentation of a downward arrow was followed by a 125 ms 'blink' period during which the screen was black. On 'valid' trials the cue pointed toward the upcoming target location while on 'invalid' trials the cue pointed opposite to the target location. On direct trials the gaze cue pointed directly toward the observer (i.e. direct gaze) and the arrow cue was a simple cross, while on 'down' trials the cue remained averted downward after the 'blink'. During null trials a fixation cross was displayed at the center of the screen for 3000 ms.

In total, there were 160 'gaze' trials, 160 'arrow' trials and 160 'null' trials divided across six time-series. There were an equal number (40) of valid, invalid, direct and down trials for both the gaze and arrow conditions. In each time-series, 28 (24 in time-series 5 and 6) null events were randomly interspersed with 26 arrow trials and 26 gaze trials (28 of each in time-series 5 and 6). In order to keep any effect of switching between arrow and gaze stimuli to a minimum, the trials were presented in a pseudo-randomized fashion such that arrow and gaze trials were presented in interleaved 'mini-blocks' that comprised 10 trials each (including null events). Subjects practiced the task outside of the scanner prior to the scanning session.

Reaction time data preprocessing and analysis

Prior to analyses, incorrect responses (an average of 3.5%) and reaction times 2.5 s.d.'s above or below the participants' mean (an average of 3%) were removed. The reaction time (RT) data were analyzed using a 2 (cue type: arrow, gaze) \times 4 (cue direction: valid, direct, down, invalid) within-subjects ANOVA. Planned simple effects contrasts included independent comparisons of cue direction for arrow and gaze trials.

Image acquisition

The blood oxygenation level-dependent (BOLD) signal was used as a measure of neural activation (Ogawa *et al.*, 1990; Kwong *et al.*, 1992). Echo planar images (EPI) were acquired with a Siemens Tim Trio scanner (Siemens, Erlangen, Germany) with a standard 'bird-cage' coil (TR 2424 ms, TE 30 ms, flip angle 78°, FOV 192 mm, matrix size 64 \times 64). Nearly whole brain coverage was achieved with 40 interleaved 3 mm axial slices and a 1 mm slice gap. In addition to the EPI series, a high-resolution anatomical image (T1-MPRAGE, TR 2500 ms, TE 4.3 ms, flip angle 8°,

matrix size 256 \times 256) was acquired for use in registering activity to each subject's anatomy and for spatially normalizing data across subjects.

fMRI preprocessing

Data were analyzed with Analysis of Functional NeuroImages (AFNI: Cox 1996) using standard preprocessing procedures. This involved six parameter 3D motion correction, slice-scan time correction, spatial smoothing with an 8-mm full-width-at-half-minimum Gaussian kernel and signal normalization to a percent signal change from the mean. Spatial normalization was accomplished using a non-linear transformation to MNI space with SPM5 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm5>).

Image analysis

Each of the six time-series was convolved with a hemodynamic response function to create a regressor for each of the eight cuing conditions. Regressors of no interest were included in the multiple regression model to factor out variance associated with mean, linear, quadratic and cubic trends in each run as well as subject head motion. Additional regressors of no interest were included to account for variance associated with any incorrect manual responses or RT outlier trials that were removed from the behavioral analysis. The regression model yielded coefficients that represented the signal change from the mean for each condition within each voxel.

For all the data analysis, experimental conditions were used as fixed factors and subjects as random factors. Events were time-locked to the cue presentation (and included the cue and subsequent target), as the timing of the paradigm precludes separating target-related activity from cue-related activity. Data were analyzed with two different approaches. In our primary analysis, a 2 (cue type: gaze, arrow) \times 2 (cue validity: valid, invalid) mixed-effects repeated-measures ANOVA was used to specifically test whether gaze and arrow cues engaged the reorienting network in a similar fashion (cf. Thiel *et al.*, 2004). We used the AlphaSim program included in AFNI to correct for multiple comparisons. A minimum cluster size of 175 27-mm³ voxels was used to achieve a corrected significance of $P < 0.05$ as determined by a Monte Carlo simulation with a voxelwise threshold of $P < 0.01$. Further analyses were performed in an effort to test whether direct gaze cues are an appropriate neutral baseline for this type of experiment. First, we did a simple contrast of direct and downward gaze cues. Second, for both gaze and arrow cues, we contrasted lateral cue trials (valid *and* invalid) with direct cue trials (note that this contrast corresponds to the 'cued-uncued' contrast in Hietanen *et al.*, 2006). Lateral and down cue trials were also contrasted. Following the method used by Hietanen and colleagues (2006), we created maps displaying the intersection of voxels from these contrasts as well as voxels unique to one or the other contrast.

Region of interest (ROI) analysis

In order to better understand the nature of the interaction effects revealed by the 2×2 ANOVA (see above), we tested simple effects on the extracted mean BOLD response for each condition averaged across voxels within given ROIs. The regions chosen represented the intersection of areas previously implicated in shifts of spatial attention (see the review by Corbetta and Schulman, 2002) that also showed a significant interaction effect of cue type \times cue validity in the current study. These were V5/MT, right posterior superior temporal sulcus/temporoparietal junction (pSTS/TPJ), right intraparietal sulcus (IPS), right somatosensory cortex and right inferior frontal gyrus (IFG).

The pSTS/TPJ was defined by creating two spheres (radius = 6 mm) centered on the two peak t -values given by the interaction in the right posterior lateral temporal cortex. All other regions were defined using the maximum probability maps (MPM) distributed in the SPM anatomy toolbox (Eickhoff et al., 2005). These included V5/MT (Wilms 2005; Malikovic et al., 2007), IFG (Amunts et al., 1999), IPS (Choi et al., 2006) and somatosensory cortex (Geyer et al., 1999, 2000).

RESULTS

Reaction times

The reaction time data are summarized in Figure 2. Analysis of the reaction times revealed a main effect of cue type (arrow vs gaze), $F(1, 15) = 18.99$, $P = 0.001$ with arrow cuing trials being significantly faster than gaze cuing trials ($M_{\text{arrow}} = 381$ ms, $M_{\text{gaze}} = 402$ ms). There was also a significant main effect of cue direction (valid vs direct vs down vs invalid), $F(3, 45) = 12.92$, $P < 0.0001$. The interaction was not significant, $P > 0.05$. For each cue type, we performed multiple comparisons between all possible pairs of cue conditions. These tests revealed that valid cues were significantly faster than direct, downward and invalid cues for both gaze and arrow cue types ($P < 0.05$). Direct gaze cues were

significantly faster than downward gaze cues ($P < 0.05$). None of the remaining pairwise comparisons revealed significant differences (P -values > 0.05).

fMRI results

In most cases the statistically significant clusters comprised many functional areas of the brain. In order to facilitate identification of functional regions, we identified significant voxels that fell within the maximum probability map of the SPM Anatomy Toolbox (Eickhoff et al., 2005). For significant voxels outside of these regions we identified local t -value maxima (minimum distance between peaks = 6 voxels).

Main effects of cue type and cue validity

Gaze trials evoked significantly greater activity than arrow trials in three large clusters of voxels. Two of these clusters represented near identical patterns in each hemisphere. These clusters extended from extra-striate visual areas into bilateral occipital-temporal and ventral temporal cortices. These same clusters also ran along a path that extended anteriorly through medial temporal regions, including the hippocampus and amygdala, and into the temporal poles. The third cluster was located primarily on the right inferior frontal gyrus and partially extended onto the right middle frontal gyrus (Supplementary Table S1). Greater activity for arrow than for gaze trials was seen in the left parietal lobe, including the IPS and postcentral gyrus. This cluster extended anteriorly just past the central sulcus into the pre-central gyrus (Supplementary Table S2).

Invalid gaze and arrow cues evoked a significantly larger response than valid gaze and arrow cues in the right lateral temporal cortex (including the pSTS/TPJ) and the right inferior parietal lobe. However, this effect was primarily driven by the arrow cues (see the description of the interaction below). A second large cluster was found in medial subcortical regions that included the putamen, pulvinar and cerebellum (Supplementary Table S3). There were no significant clusters revealed by contrasting valid vs invalid.

Interaction of cue type and cue validity: differential activation of the reorienting network

A 2 (cue type: gaze, arrow) \times 2 (cue validity: valid, invalid) ANOVA revealed a significant interaction in five clusters including the right IFG, bilateral IPS and bilateral occipital/occipitotemporal cortices (Supplementary Table S4).

ROI analysis

The results of the interaction were expanded on by an ROI-based analysis. Figure 3A shows the location and pattern of response of all ROIs where the signal change was extracted. These were located in the right IFG, right IPS, right TPJ, right primary somatosensory cortex and right V5/MT. Simple effects tests (see Table 1) revealed that the interaction was driven by invalid arrows evoking a

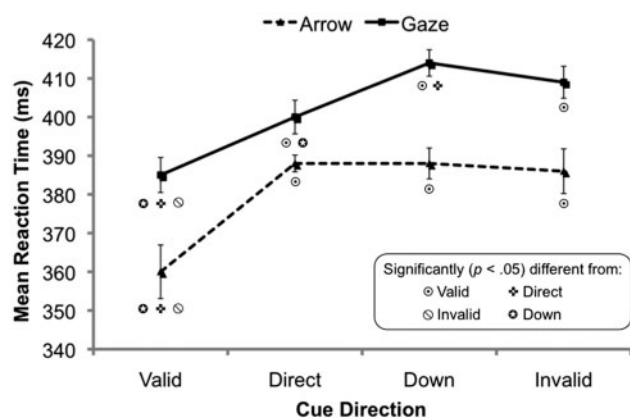


Fig. 2 Means and standard errors (in ms) of manual reaction times for reporting the appearance of the peripheral target as a function of cue type (arrow, gaze) and cue direction (valid, direct, down, invalid).

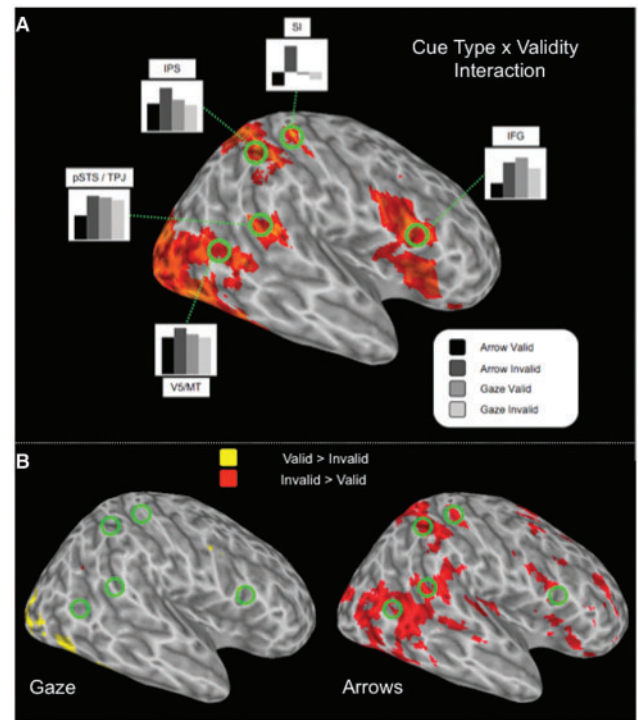


Fig. 3 (A) Voxels showing a significant interaction effect of cue type (gaze, arrow) and cue validity (valid, invalid). Regions include those previously implicated during reorienting to unattended targets: IPS, intraparietal sulcus; IFG, inferior frontal gyrus; TPJ, temporo-parietal junction and those implicated during preparatory shifts of attention: SI, primary somatosensory cortex; V5/MT. Bar graphs display the signal change in each of the four conditions at the peak voxel within each region. (B) Overlay showing both of valid > invalid (yellow) and invalid > valid (red) contrasts for gaze (left) and arrow (right) cues. Only those voxels significant at $P < 0.01$, uncorrected are displayed. Left: Overlay showing the two contrasts for gaze cues. Right: Overlay showing the two contrasts for arrow cues.

Table 1 ROI results

Regions defined by locating local maxima			
Region	Interaction F	Arrow invalid > Valid	Gaze invalid > Valid
IPS	11.01*	4.01*	0.97
IFG	22.13*	3.31*	1.76
Somatosensory cortex	15.46*	4.93*	1.07
V5/MT	4.46*	2.59*	0.78
Lateral temporal cortex	15.39*	5.44*	0.73

Results of simple effects tests on the extracted mean BOLD response for each condition averaged across voxels within ROIs. ROIs represent areas previously implicated in shifts of spatial attention that also showed a significant interaction between cue type and cue validity in a 2×2 ANOVA ($P < 0.05$, corrected, $N = 16$) (see Materials and methods section).

* $P \leq 0.05$.

significantly greater response than valid arrows in all ROIs (P -values ≤ 0.05), whereas there was no significant difference between invalid gaze and valid gaze (P -values > 0.05). This pattern was largely preserved outside of the ROIs as well.

In other words, there were no significant clusters in the brain for valid gaze vs invalid gaze, whereas valid arrows vs invalid arrows resulted in multiple activated regions. However, small clusters of activity for valid gaze > invalid gaze in early visual and ventral temporal cortices were revealed when using a more liberal statistical threshold ($P < 0.01$, uncorrected, see Figure 3B).

Lateral cues vs direct or down baseline

Lateral arrow cues (i.e. valid and invalid) contrasted with non-directional direct cues showed significantly greater activity in bilateral occipital, occipitoparietal (including the superior parietal lobe and intraparietal sulcus) and right lateral temporal cortices, whereas contrasting lateral arrow cues to downward arrow cues revealed no significant differences. Conversely, lateral gaze cues contrasted with direct gaze revealed no significant differences, whereas contrasting lateral gaze cues to downward gaze cues showed significantly greater activity in bilateral occipital and ventral temporal cortices as well as the right precuneus, superior parietal lobe and intraparietal sulcus. Contrasting direct and downward gaze cues did not reveal any significant BOLD response differences (Supplementary Figure S1).

DISCUSSION

The main finding of the current study is that the brain's response when spatially orienting to non-predictive spatial cues is different for social eye gaze cues than symbolic arrow cues. Reaction time data showed that both gaze and arrow cues were effective in triggering seemingly reflexive shifts of spatial attention. However, trials with invalid arrow cues resulted in a stronger hemodynamic response in the ventral 'reorienting' attention network than those including valid arrow cues. No such difference was seen during trials including valid and invalid gaze cues (Figure 3B). Broadly, these data show that arrow cues engage the ventral reorienting network differently than gaze cues. Further, we found that contrasting lateral cues with direct cues evoked a different activation pattern than did contrasting lateral cues with downward cues; this is an important methodological distinction for future investigations. In what follows, we will discuss these findings in detail and relate them to previous neuroimaging and cognitive studies on voluntary and reflexive and gaze-cued orienting of visual attention.

The engagement of the ventral attention network by gaze and arrow cues

Previous studies on the ventral attention network have quantified it by assessing the effects of cues and targets separately (e.g. Corbetta *et al.*, 2000), or by contrasting invalidly cued trials with validly cued trials (Thiel *et al.*, 2004). We followed the latter approach with the exception that cue type (gaze vs arrow) was used as an additional factor in the ANOVA. The main effect of validity (Supplementary Table S1) shared multiple regions with those reported by Thiel and colleagues

(2004), including the right pSTS/TPJ (cf. right middle temporal gyrus and right supramarginal gyrus) and the right inferior parietal lobe (cf. right parietal operculum). An interaction analysis yielded a network of clusters including the right pSTS/TPJ and the right IFG, the core components of the ventral attention network, as well as the right IPS, an area in the dorsal attention system that is often engaged by both reflexive and voluntary orienting of attention (Corbetta and Shulman, 2002). However, a surprising trend was observed when the interaction was broken down by ROI analyses. The visual and attention networks in the brain responded differentially to invalid *vs* valid arrow cues but not invalid *vs* valid gaze cues. Specifically, the results for the arrow cuing show that invalid *vs* valid arrows increased activity in the ventral attention network whereas no such difference was noted for invalid *vs* valid gaze cues (Figure 3B). Indeed, the average response within regions of this network evidenced a trend (although nonsignificant) toward a larger response for valid than invalid gaze cues. This pattern of results implies that gaze and arrow cues, despite similar behavioral effects, engage the attentional systems differently.

A recent study by Hietanen and colleagues (2008) suggests that gaze and arrow cues differentially recruit the dorsal (i.e. voluntary) and ventral (i.e. reflexive) frontoparietal attention networks. They measured event-related potentials (ERPs) to centrally presented gaze and arrow cues and found that arrow but not gaze cues resulted in the early directing attention negativity (EDAN) component associated with voluntary orienting of attention (Harter *et al.*, 1989; Yamaguchi *et al.*, 1994). Importantly, both cue types were equally effective in shifting visual attention, as indexed by both manual RTs and target-triggered N1 and P1 components. Hietanen and colleagues proposed that the source of the EDAN might be the dorsal frontoparietal attention network thus demonstrating a strong engagement of this system by arrows cues whereas the null effect for gaze cues could represent a disproportionate reliance on the reflexive frontoparietal network.

The current data, in light of the previous findings of Hietanen and colleagues, can be interpreted as suggesting that the dorsal and ventral attention networks were similarly recruited by valid and invalid gaze cues. As illustrated in Figure 3B, no differences in the activity of the attention systems were observed when the valid and invalid gaze cues were contrasted with each other, although behavioral data (Figure 2) confirms that gaze cues were indeed successful in inducing attention shifts. Together these data thus suggest that the onset of a gaze cue engages the ventral attention network, whose activity would remain high regardless of the subsequent target location (valid *vs* invalid). Indeed, an examination of the response to gaze cues reveals little difference between them in both the dorsal and ventral attention systems (Supplementary Figure S2). In contrast, the onset of an arrow cue would initially engage the dorsal

attention system. The ventral system would only be recruited if the subsequent target appeared at the 'invalid' location, causing a stimulus-driven reorienting to the target. Consistent with this, an examination of the response to arrow cues reveals a more pronounced difference between valid and invalid cues in the ventral than in the dorsal attention system (Supplementary Figure S2). However, this difference offers only indirect evidence to support our interpretation. To directly test this hypothesis additional studies will be necessary. Specifically, for both cue types, it will be necessary to be able to independently estimate the hemodynamic response to the cue and to the target. For the gaze condition, it will be crucial to use a common baseline that is not likely to induce its own attentional response (see below).

Alternatively, the lack of gaze cue modulation of the BOLD response in the attention network could be due to excitatory and inhibitory neural responses cancelling each other out. Shepherd and colleagues (2009) have shown that some neurons in macaque lateral intraparietal area (LIP) increase their firing rate, while others reduce their firing rate, when the monkey views an image of a conspecific gazing toward the cell's response field. If cells with similar response properties exist in intermixed clusters in humans, contrasting BOLD responses to valid and invalid gaze cues could potentially result in a net null effect as observed in the present study. However, high temporal coherence was noted only in those neurons that increased rather than decreased their firing rate. The low temporal coherence of the suppressive effect would exert less influence on downstream local field potentials and, therefore, less influence on the evoked hemodynamic response (Logothetis, 2002), making it less likely that these responses could cancel each other out.

The current findings support the 'specialness' of gaze cues by demonstrating that they achieve reflexive orienting of attention primarily via different cortical systems than arrow cues, and seemingly with less processing demand (as indexed by BOLD response) than arrows. The human eye is unique among primates in that it has a large and bright sclera, which increases the visibility of the pupil and iris. Kobayashi and Kohshima (1997) have suggested that the human eye has evolved these features to signal gaze direction (i.e. locus of attention) to others. This notion is bolstered by evidence that infants as young as 2–5 days old discriminate gaze contact and gaze aversion (as indexed by ERPs; Farroni *et al.*, 2002) and will automatically orient to gaze cues as early as 10 weeks old (Hood, 1998). The brain, then, might be sensitized to gaze in the same way it is to strong low-level sensory stimuli such as a loud sound or a bright light. This sensitization could operate in parallel with learned contingencies. Arrow cuing, on the other hand, relies solely on learned contingencies. This could account for more 'reflexive' brain effects to gaze direction despite near indistinguishable behavioral effects to gaze and arrow cues. Despite the

overt similarities, gaze and arrow cues are thus processed differently in the brain.

Attentional effects of 'direct' cues

The contrast of lateral arrow *vs* direct arrow cues yielded significant differences in expansive regions of occipitotemporal and occipitoparietal cortices. A similar effect was not observed for the gaze stimuli. This result largely replicates the findings of Hietanen *et al.* (2006). Importantly though, replacing the direct cues with downward cues in the contrast resulted in a striking reversal of the pattern of results. That is, occipitotemporal and occipitoparietal regions were again shown to be active (though with a right hemisphere bias); however, the differences were now significant for the gaze, but not arrow, trials. Why would two seemingly irrelevant cues (i.e. neither ever cued the location of the subsequent target) evoke such disparate results? It is possible that the effects of direct gaze cues are driven by their ability to capture attention (von Grünau and Anston 1995) as well as their visual salience and social relevance (Batki 2000; Farroni *et al.*, 2002; Mason *et al.*, 2004; Farroni *et al.*, 2006). However, these differences were not large enough to be seen when directly contrasting direct and downward cues. Alternatively, it seems that direct gaze is perceived as a directional, rather than a nondirectional, cue and would therefore engage the same orienting response as lateral cues.

Unlike direct gaze cues, direct (or neutral) arrow cues *are* an appropriate baseline for arrow cuing given that they convey no spatial information and, therefore, do not affect target detection RTs or BOLD responses within the brain's attention network. It is this differential effect of gaze and arrow 'neutral' cues on the BOLD response that is particularly problematic with regard to prior fMRI studies of social *vs* symbolic cuing. We suggest that future studies that include a 'neutral' baseline rather than contrasting valid trials to invalid trials use either truly non-directional cues (e.g. closed eyes and non-directional arrows) or matched directional cues that are never predictive of stimulus location (e.g. downward gaze and arrow cues).

CONCLUSIONS

These findings support the notion that the facilitation of target detection by gaze cues and arrow cues is subserved by different neural responses in the attention systems. We have shown that arrow cue validity modulates the activity in the ventral frontoparietal attention network (specifically, the right TPJ and IFG) and the IPS. Importantly, we found no such modulation as a function of validity for centrally presented gaze cues, suggesting that orienting of spatial attention is supported by different neural systems for social gaze and symbolic arrow cues. Further, we have shown that the baselines often used in arrow and gaze cuing paradigms (i.e. a line segment and a direct-gaze face) are not equivalent and should be interpreted accordingly. Although a line segment faithfully represents the absence of an attentional cue, the

same cannot be said of a direct-gaze, perhaps due to its strong social relevance.

SUPPLEMENTARY DATA

Supplementary Data are available at SCAN Online.

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